

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF  
CHENG ET AL.

APPLICATION NO: Division of Application Serial No. 09/812,960 Filed March 20, 2001

FILED: Herewith

FOR: SUBSTITUTED ACID DERIVATIVES USEFUL AS ANTIDIABETIC AND ANTI OBESITY  
AGENTS AND METHOD

Assistant Commissioner for Patents  
Washington, D.C. 20231

PREEXAMINATION AMENDMENT

Sir:

Please amend the above-identified application to read as follows.

In the Specification:

Page 1, line 4, after "this" and before "is", please insert -- is a division of U.S. application  
Serial No. 09/812,960 filed March 20,2001, which --

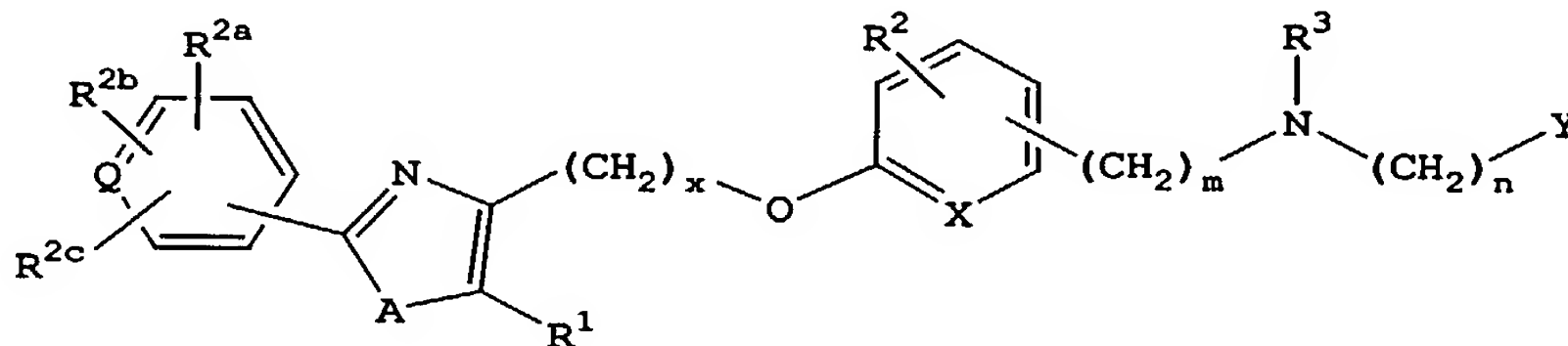
line 5, after "2000" and before "which", please insert -- , now abandoned, -- .

In the Claims:

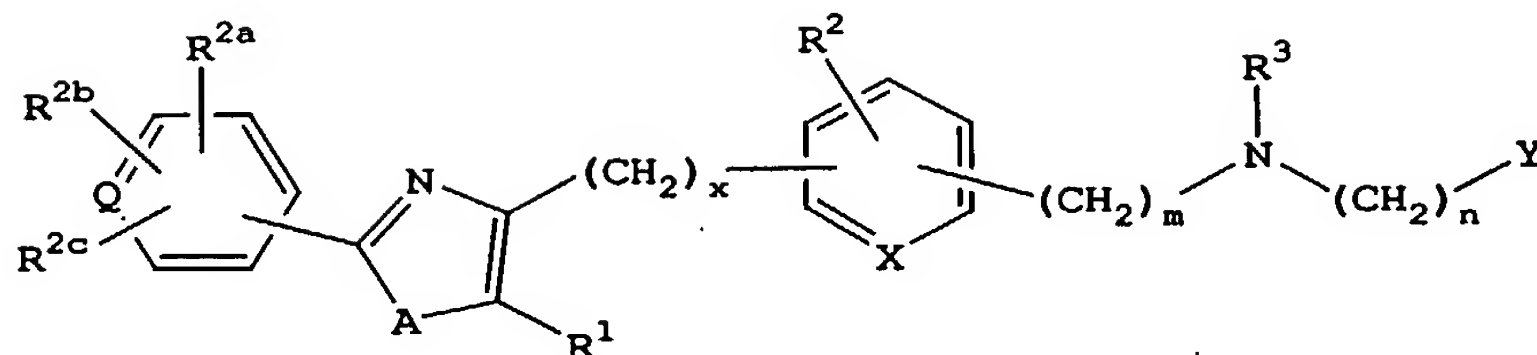
Please cancel Claims 1, 6 to 9, 11 to 13, 15, 19, 23 to 25, 29, 33, 35, 36, 38, 41 to 49 and  
51 to 54.

Please amend Claims 2 to 5, 10, 14, 16 to 18, 20 to 22, 26 to 28, 30 to 32, 34, 37, 39, 40  
and 50 as follows.

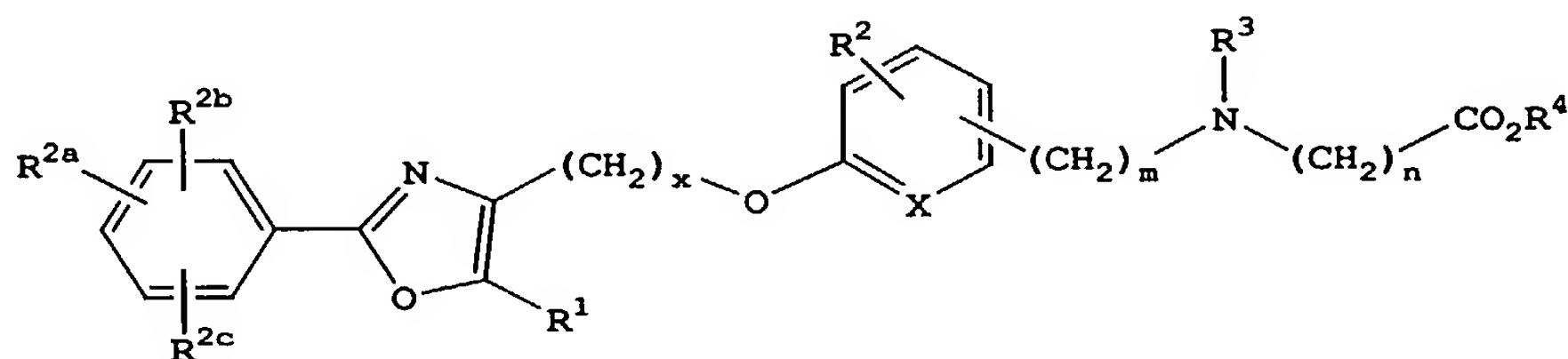
--2. (Amended) The method as defined in Claim 34 wherein the compound employed  
has the structure



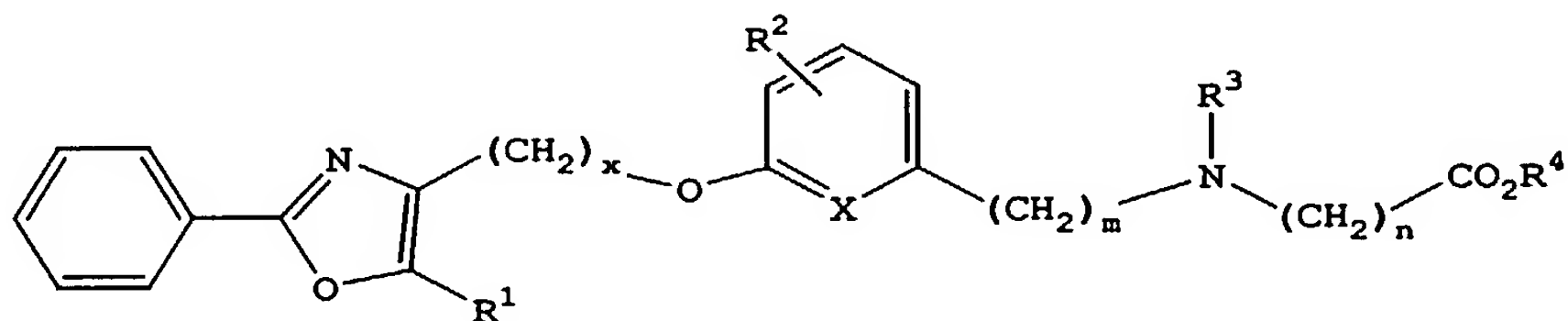
or



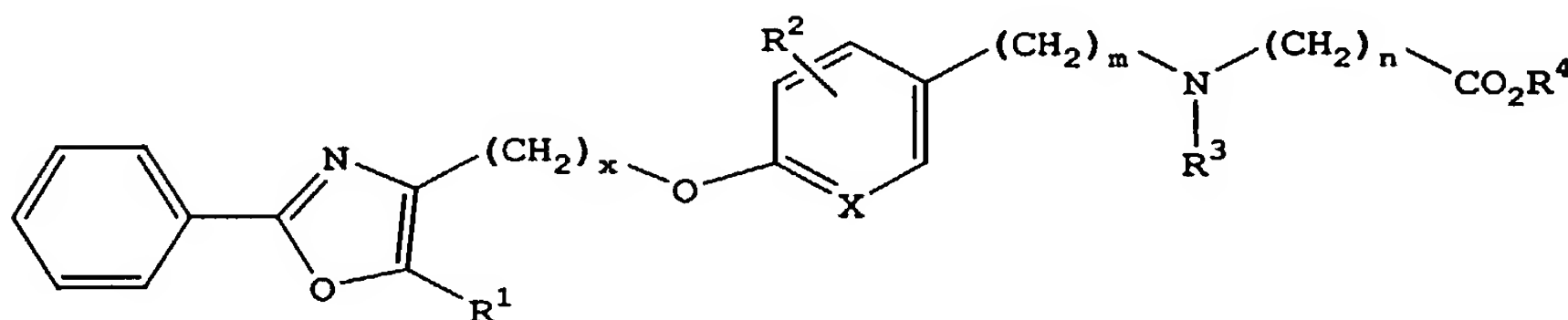
--3. (Amended) The method as defined in Claim 34 wherein the compound employed has the structure



--4. (Amended) The method as defined in Claim 34 wherein the compound employed has the structure



or



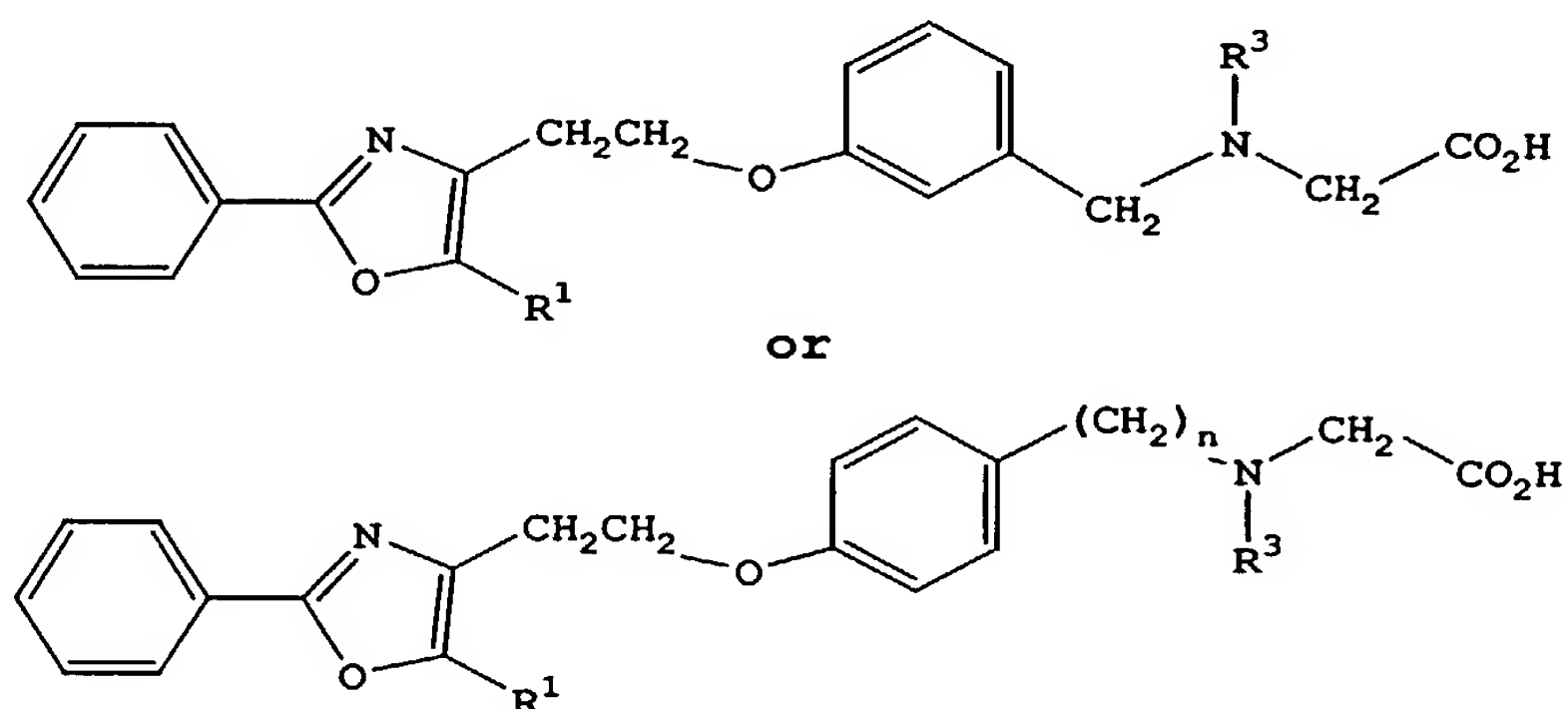
--5. (Amended) The method as defined in Claim 34 where in the compound employed (CH<sub>2</sub>)<sub>x</sub> is alkylene, alkenylene, allenyl, or alkynylene. --

--10. (Amended) The method as defined in Claim 34 where in the compound employed

(CH<sub>2</sub>)<sub>x</sub> is CH<sub>2</sub>, (CH<sub>2</sub>)<sub>2</sub>, (CH<sub>2</sub>)<sub>3</sub>, or  $\begin{array}{c} \text{CH}_3 \\ | \\ \text{---C---} \\ | \\ \text{CH}_3 \end{array}$ , (CH<sub>2</sub>)<sub>m</sub> is CH<sub>2</sub>, or  $\begin{array}{c} \text{R}_a \\ | \\ \text{---CH---} \end{array}$  where R<sub>a</sub> is alkyl or alkenyl, (CH<sub>2</sub>)<sub>n</sub> is CH<sub>2</sub>, R<sup>1</sup> is lower alkyl, R<sup>2</sup> is H, R<sup>2a</sup> is H, R<sup>4</sup> is H, and R<sup>3</sup> is arylalkyloxycarbonyl,

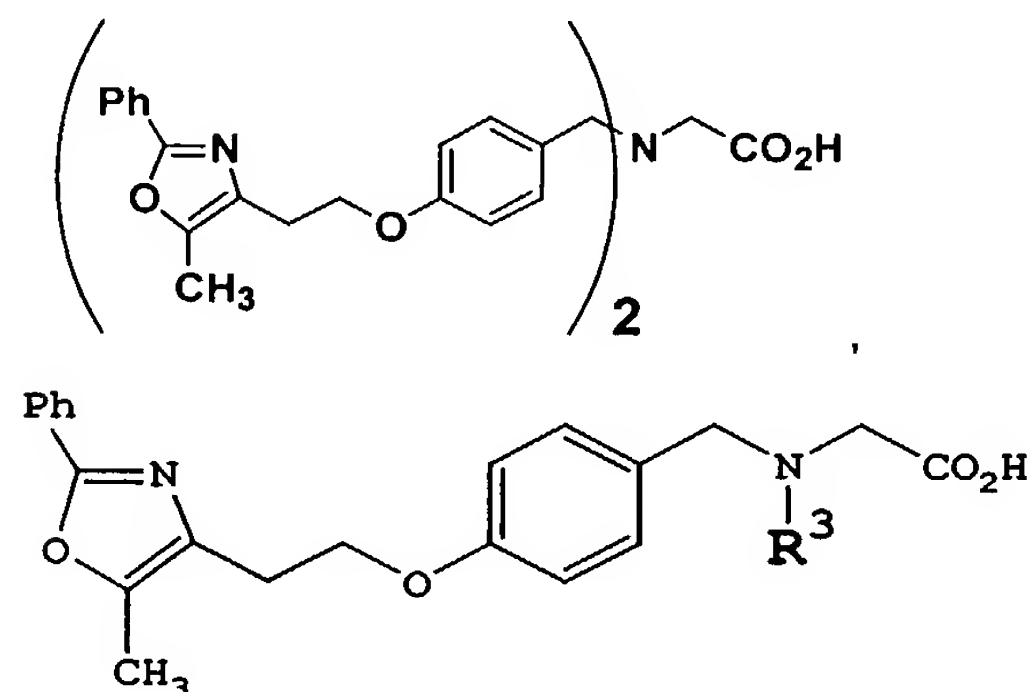
aryloxycarbonyl, haloaryl-oxycarbonyl, alkoxyaryloxycarbonyl, alkylaryloxycarbonyl, aryloxyaryloxycarbonyl, heteroaryloxyarylalkyl, heteroaryloxycarbonyl, arylalkenyloxycarbonyl, cycloalkylaryloxycarbonyl, cycloalkyloxyaryloxycarbonyl, alkyloxyaryloxycarbonyl, arylalkylsulfonyl, arylalkenylsulfonyl, arylthiocarbonyl, cycloheteroalkylalkyloxycarbonyl, cycloheteroalkyloxycarbonyl, or polyhaloalkylaryloxycarbonyl, which may be optionally substituted. --

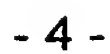
--14. (Amended) The method as defined in Claim 34 where the compound employed has the structure

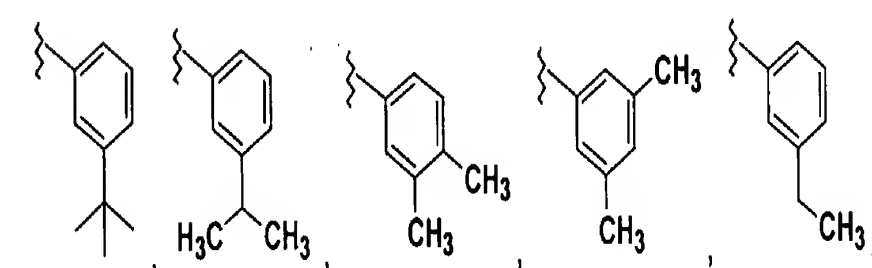
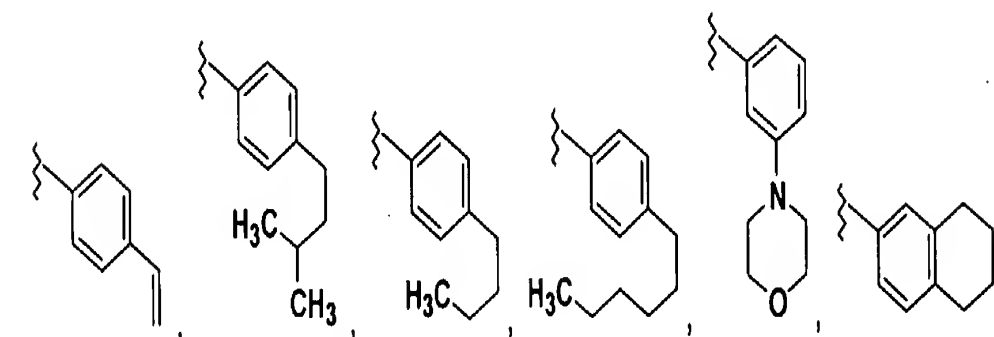
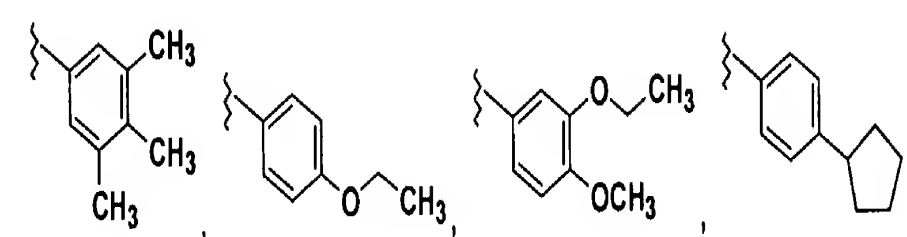
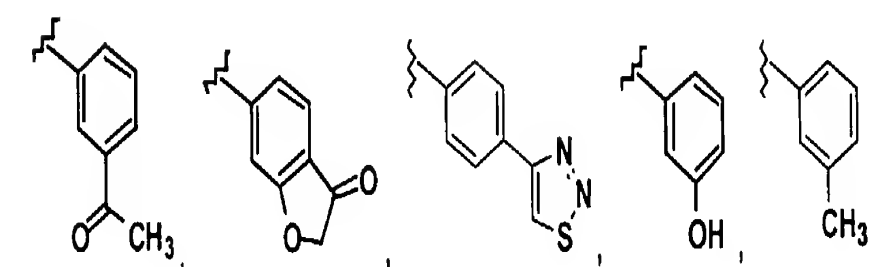
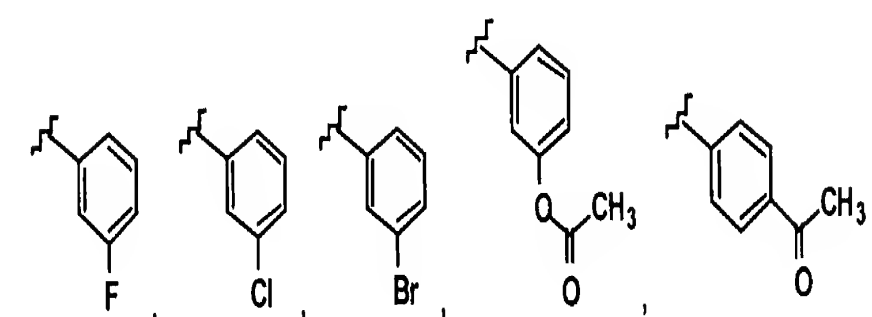
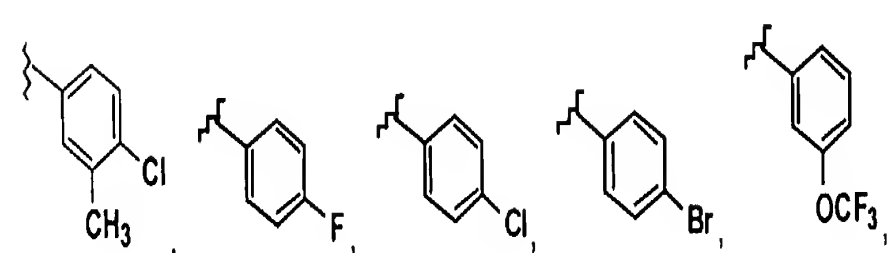
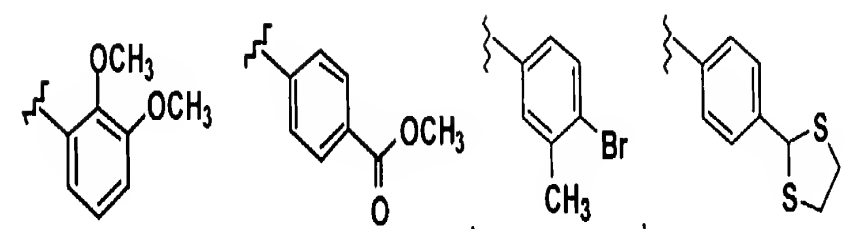
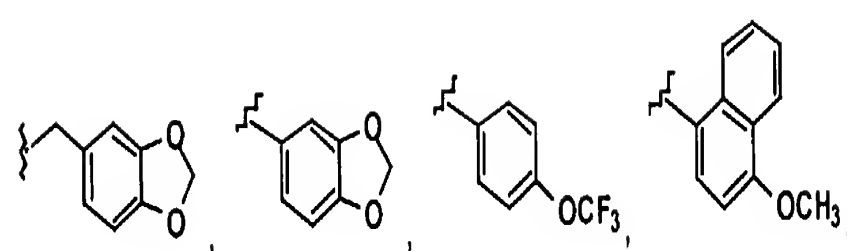
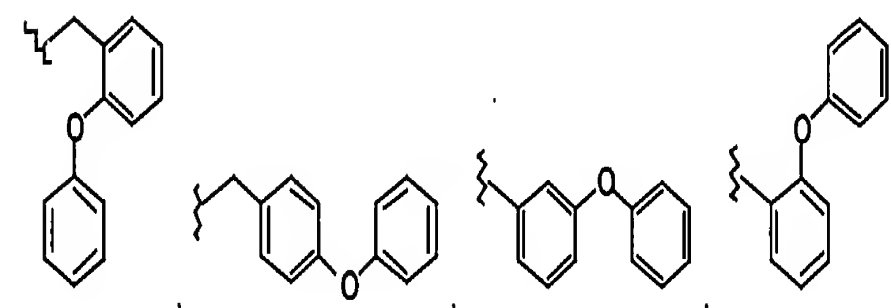
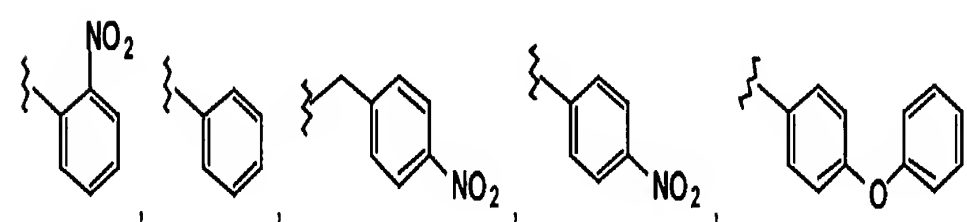
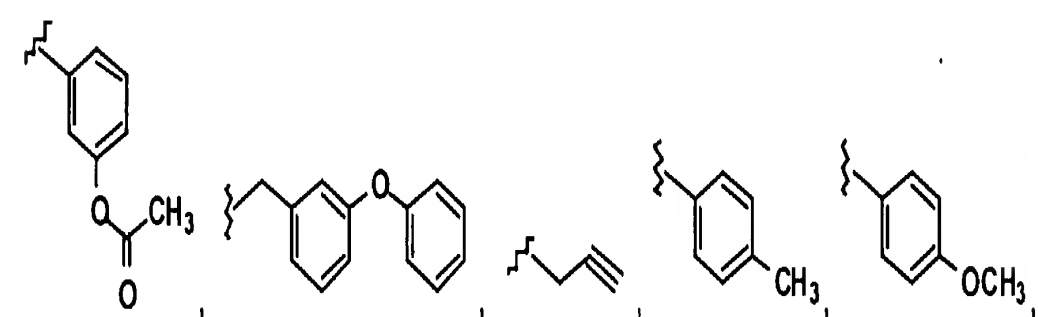
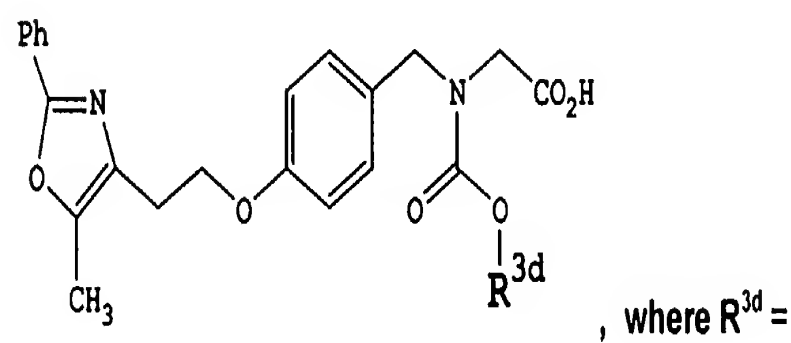
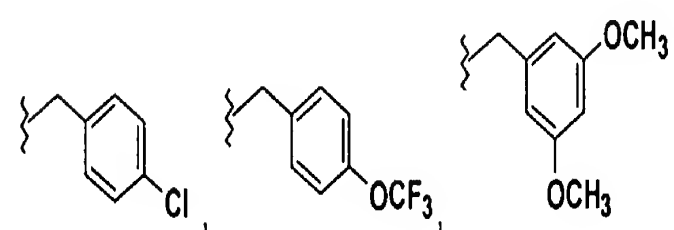
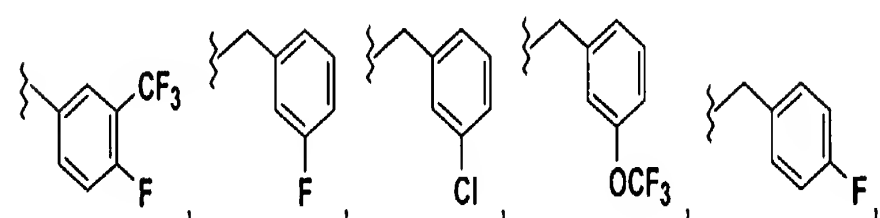
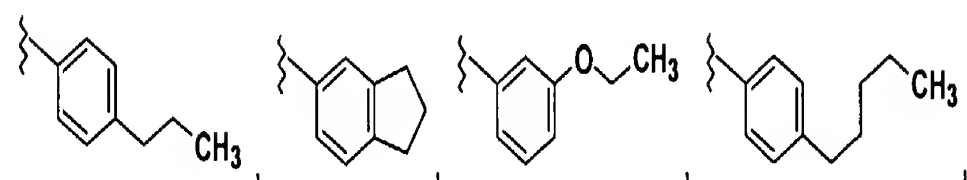
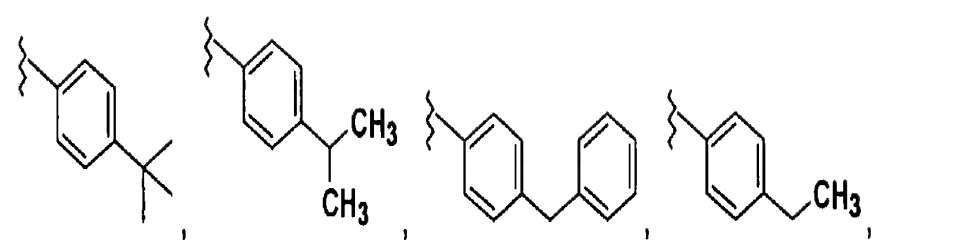


where  $(CH_2)_n$  is  $CH_2$  or  $\begin{array}{c} CH_3 \\ | \\ -CH- \end{array}$ . --

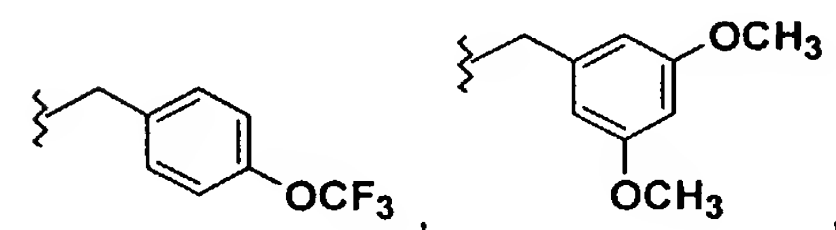
--16. (Amended) The method as defined in Claim 34 wherein the compound employed has the structure







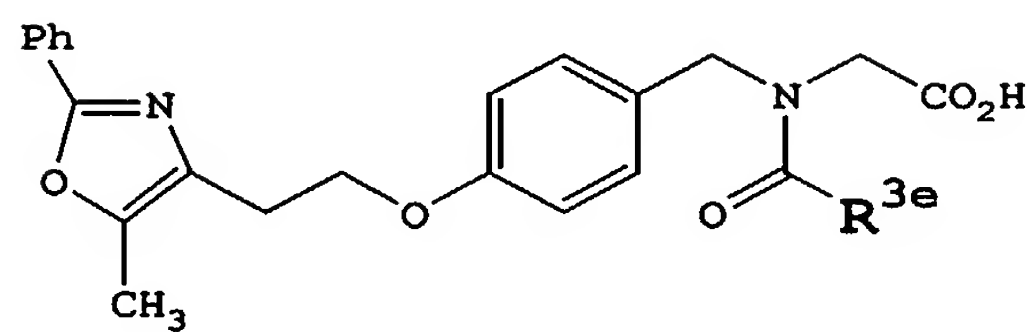
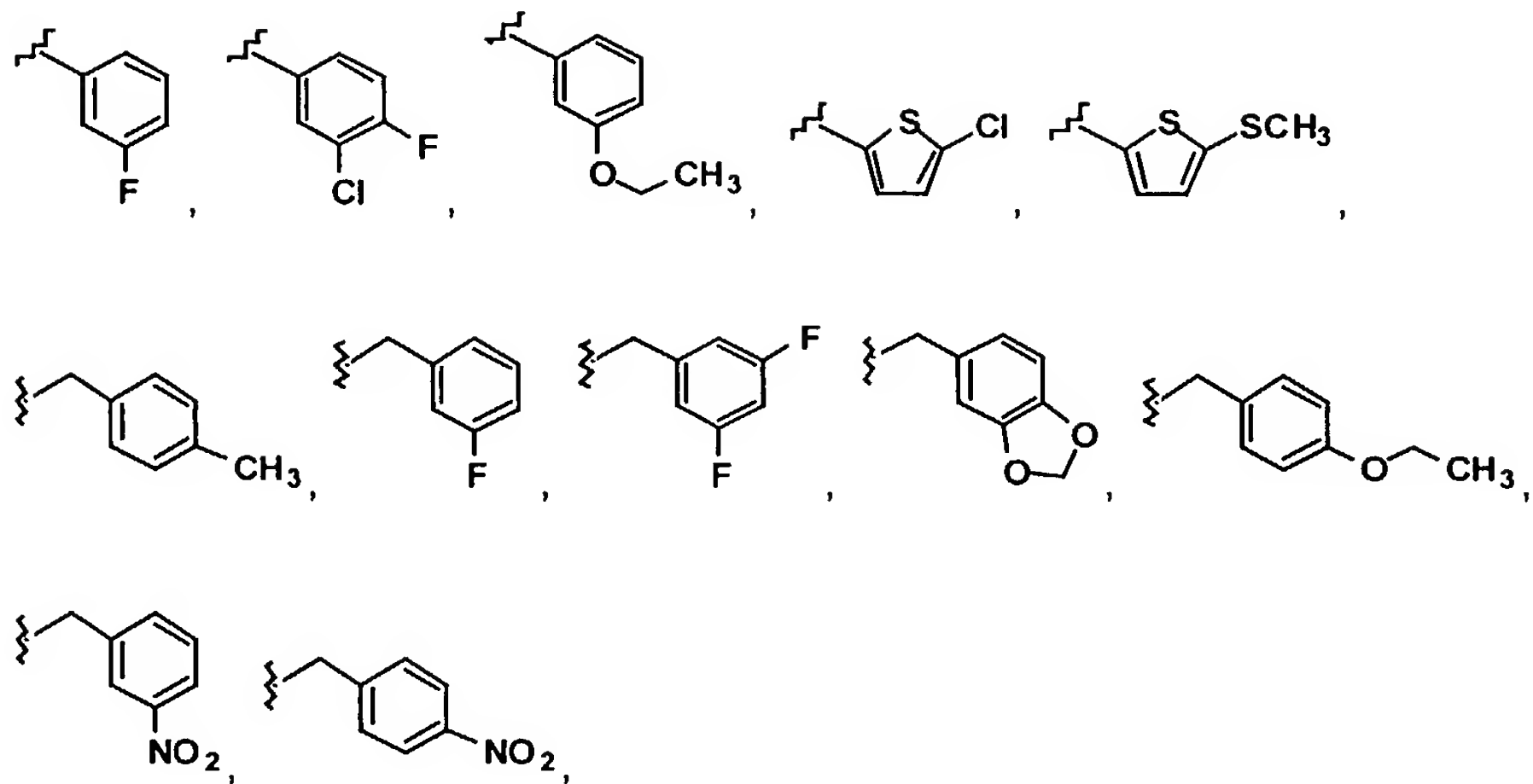




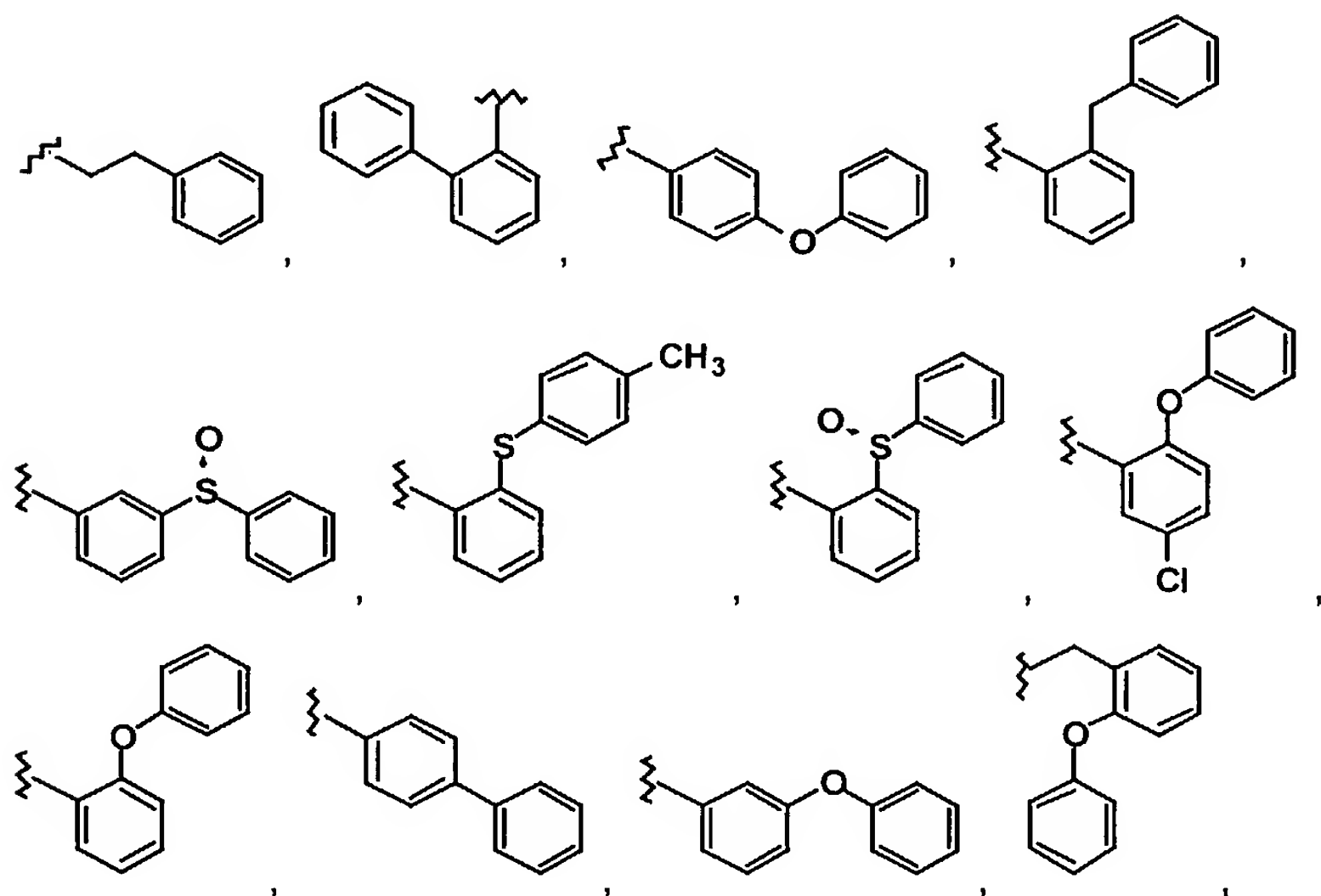


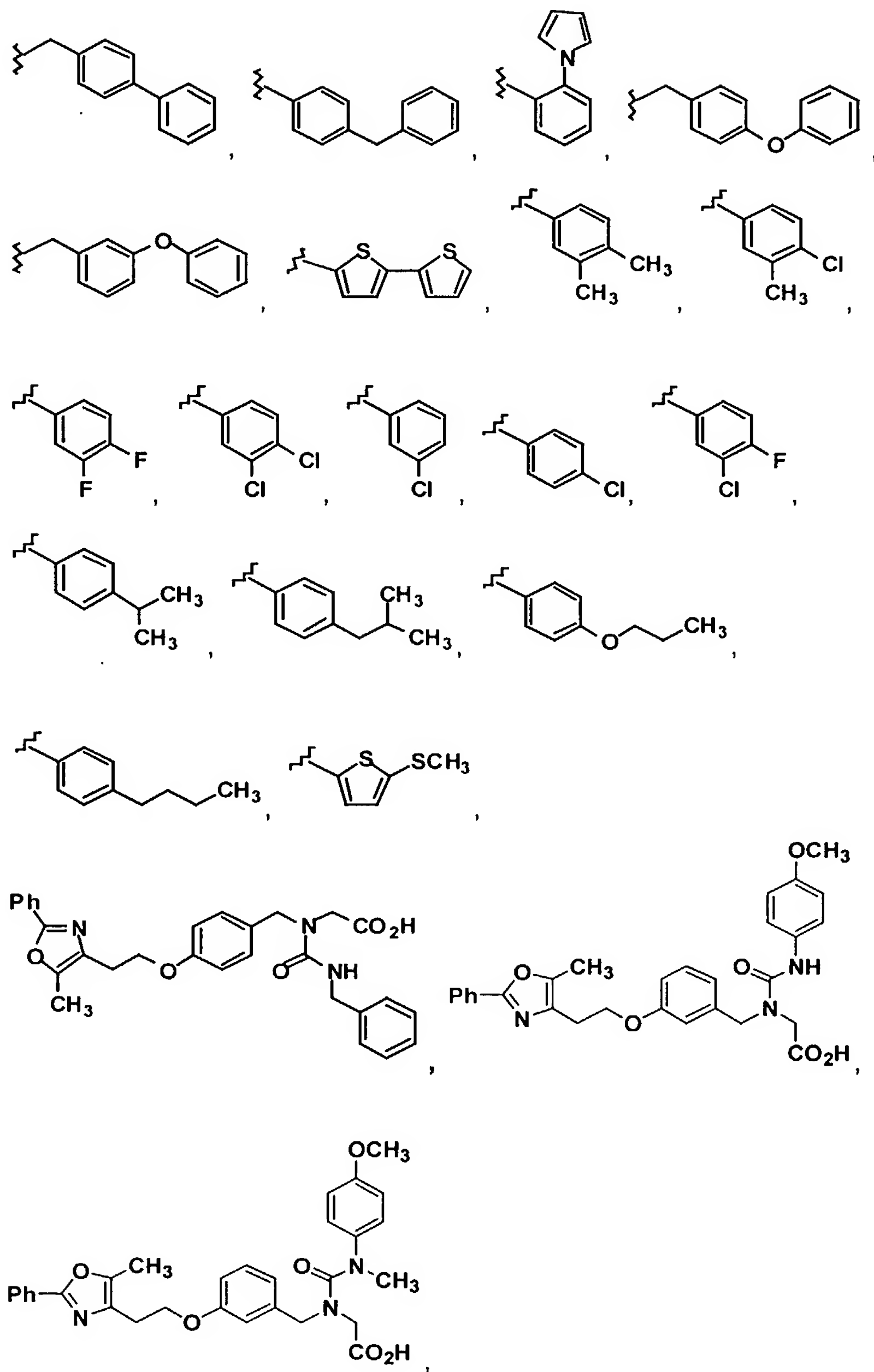


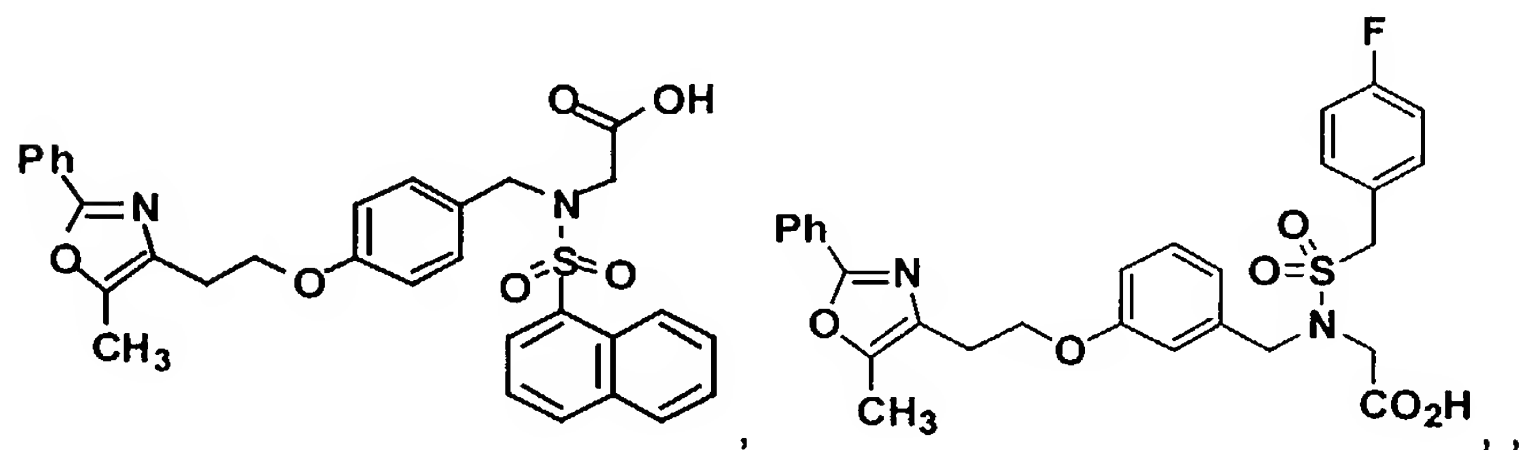
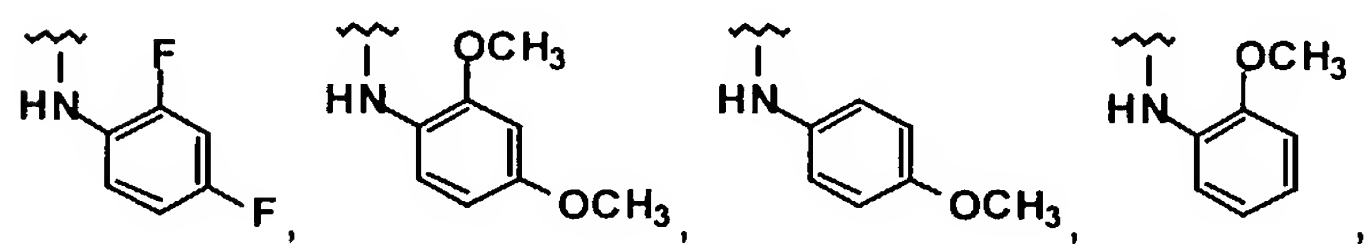
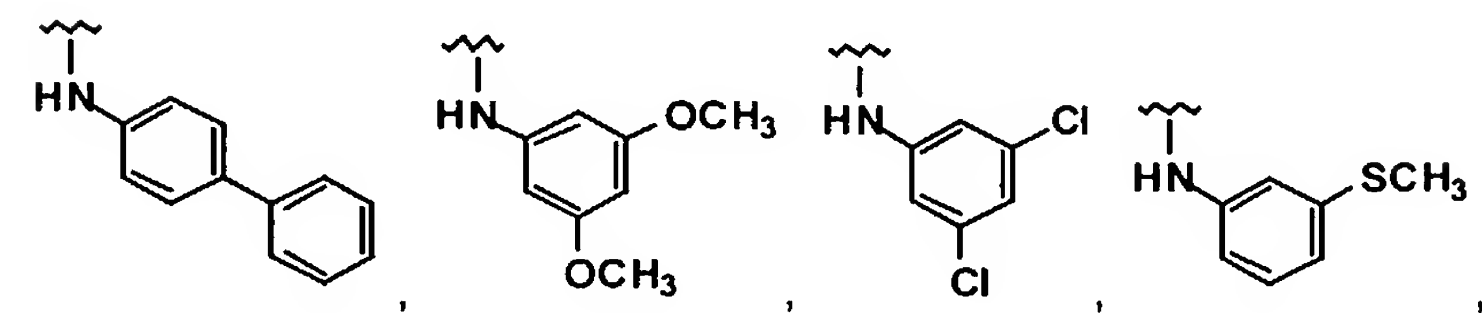
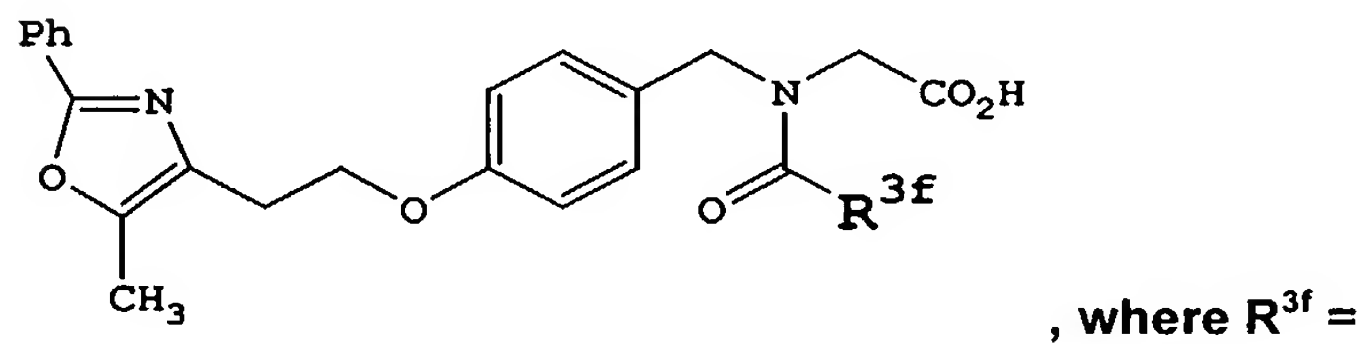
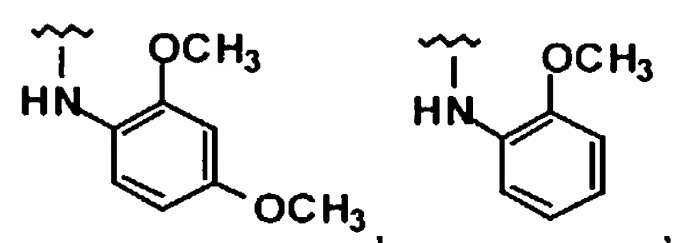
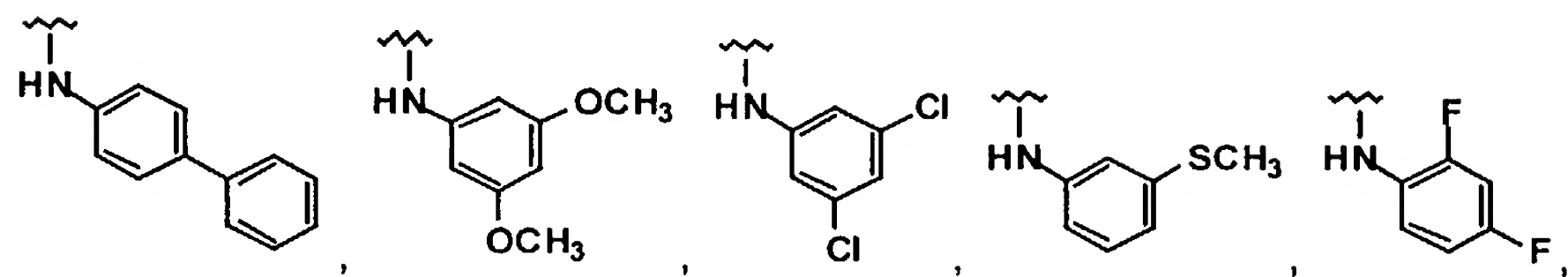
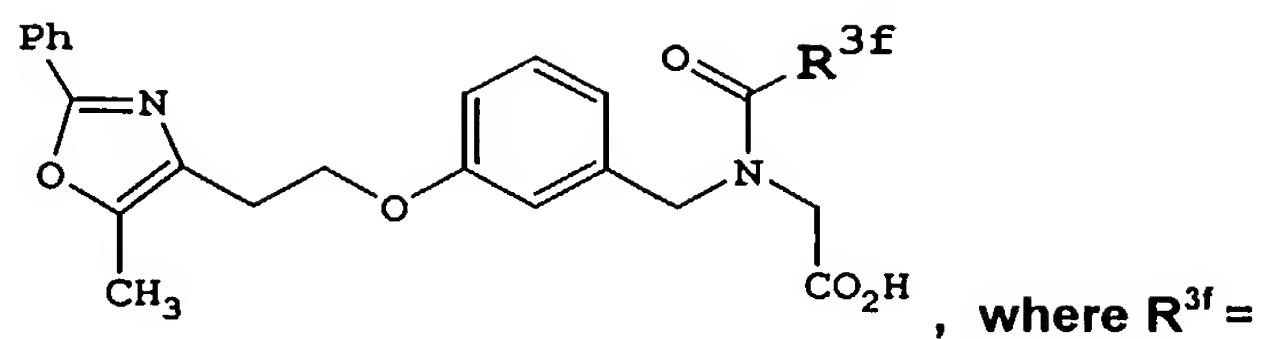


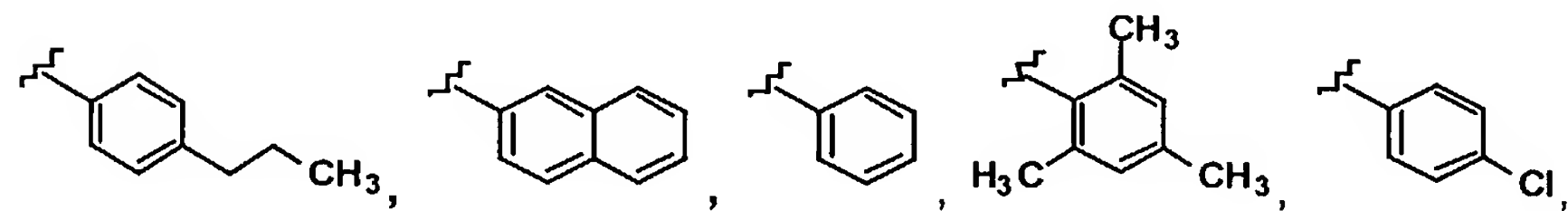
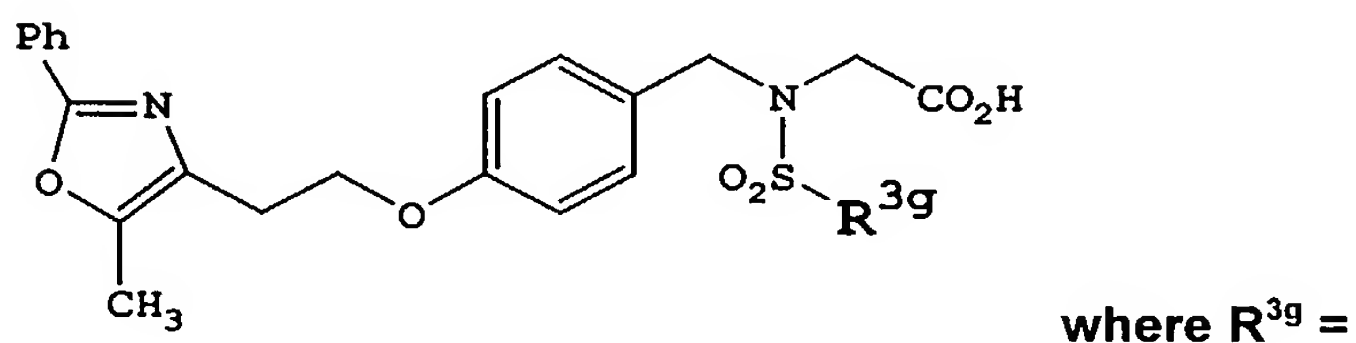
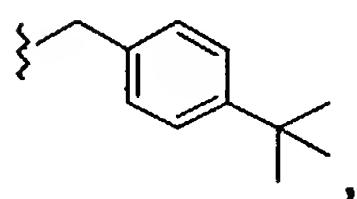
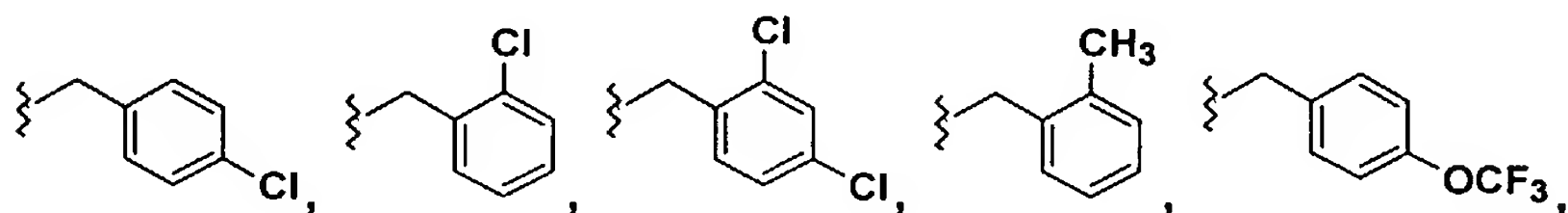
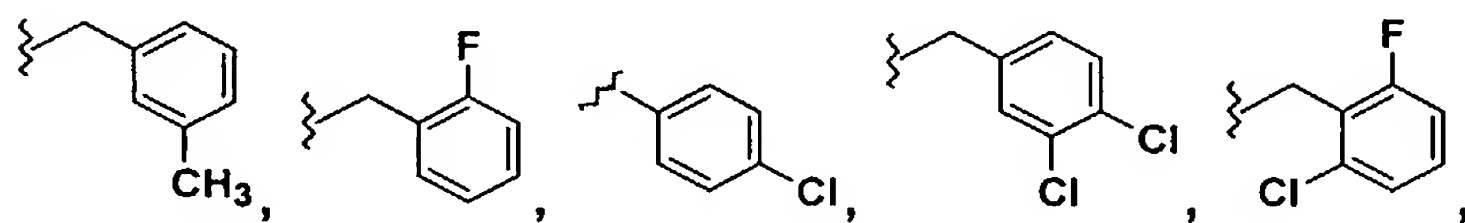
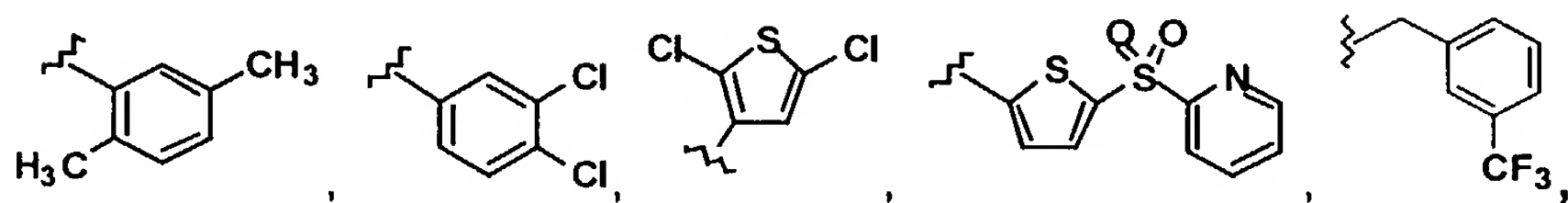
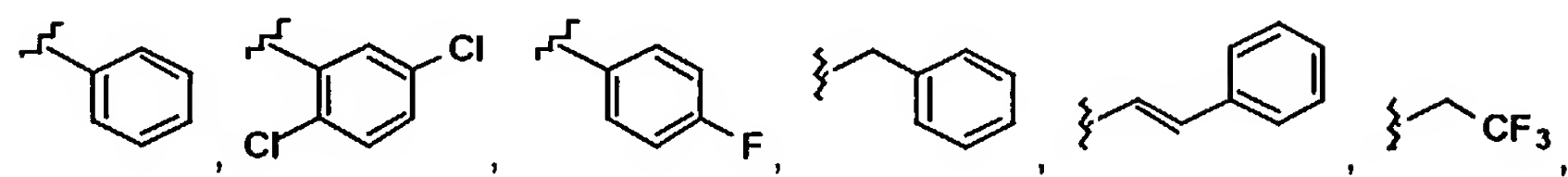
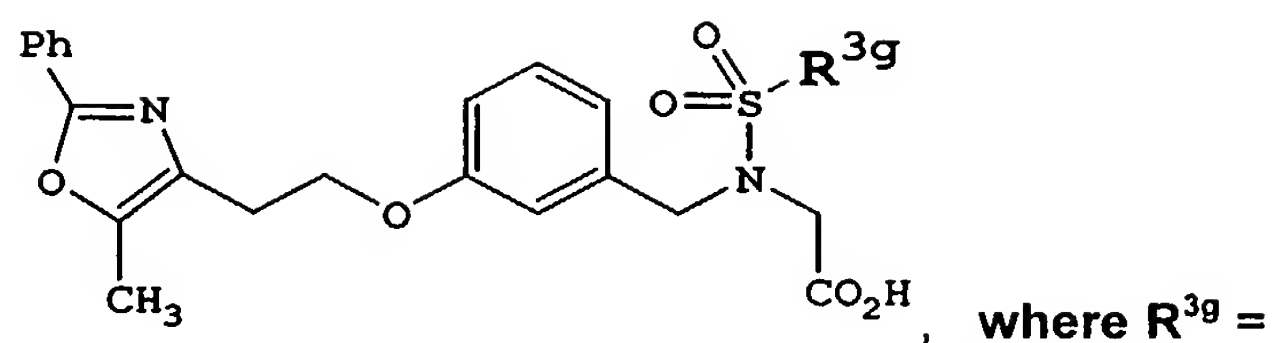


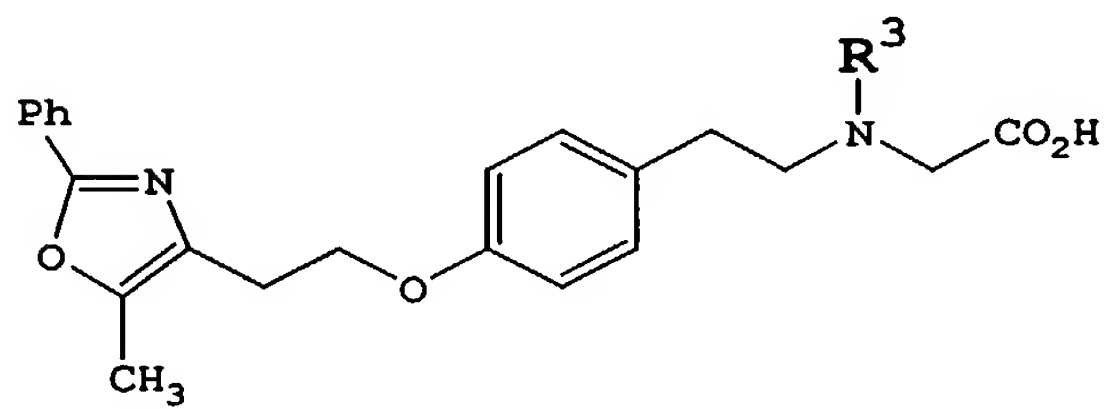
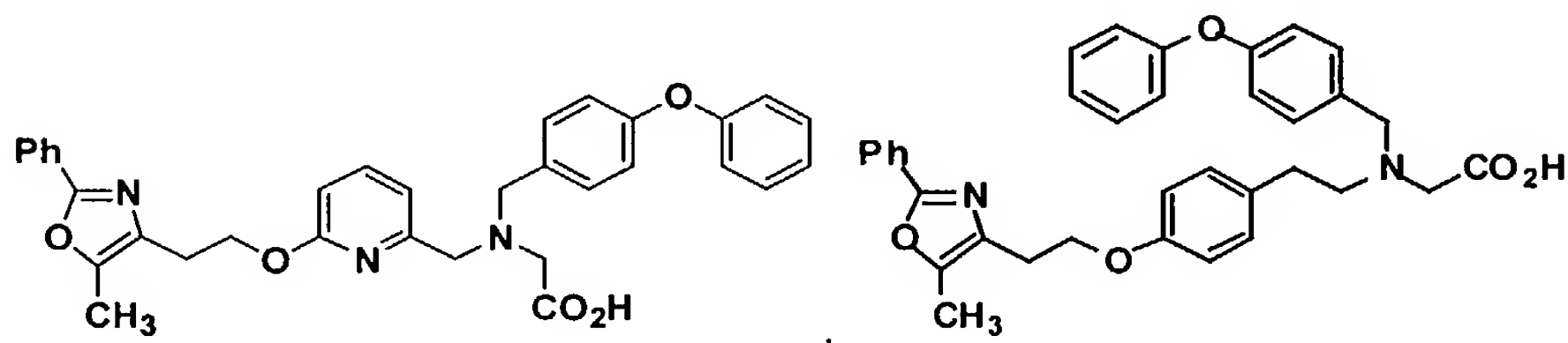
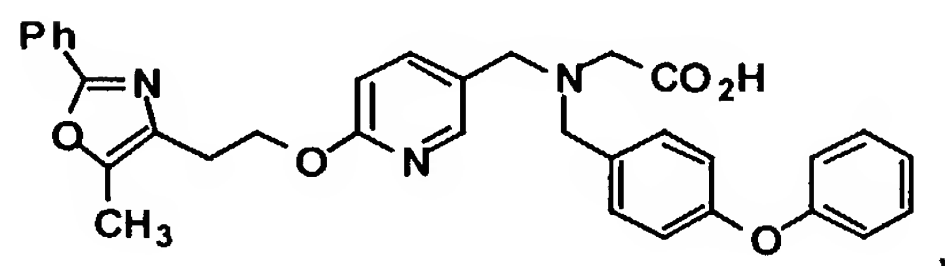
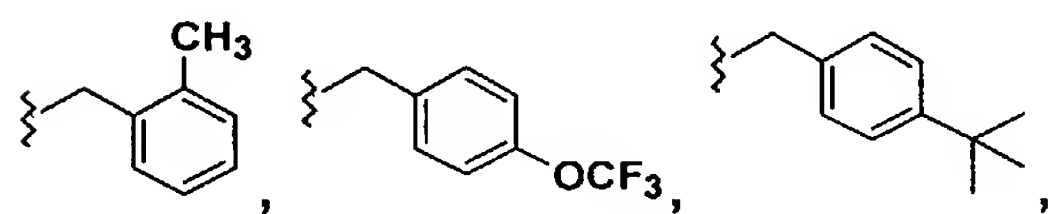
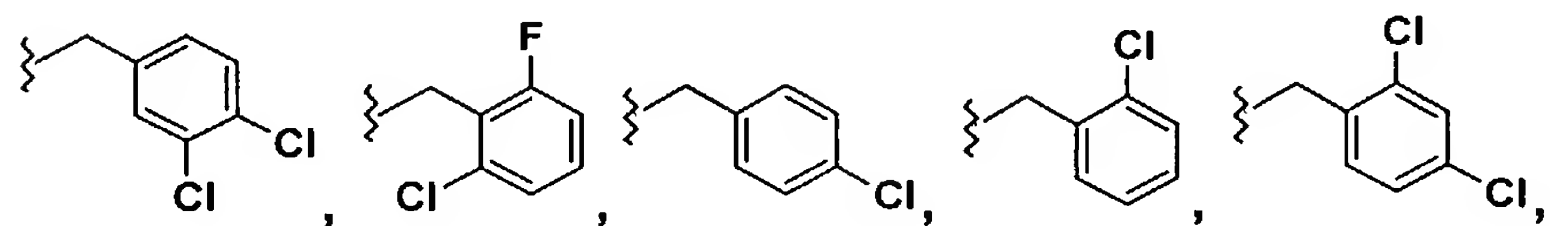
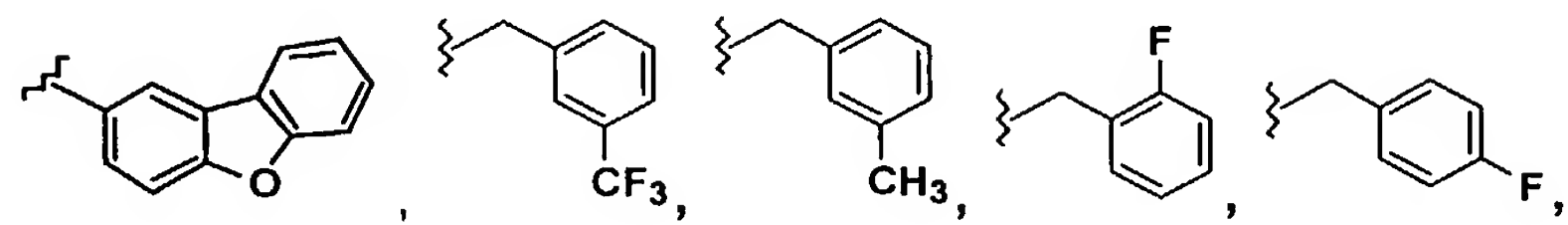
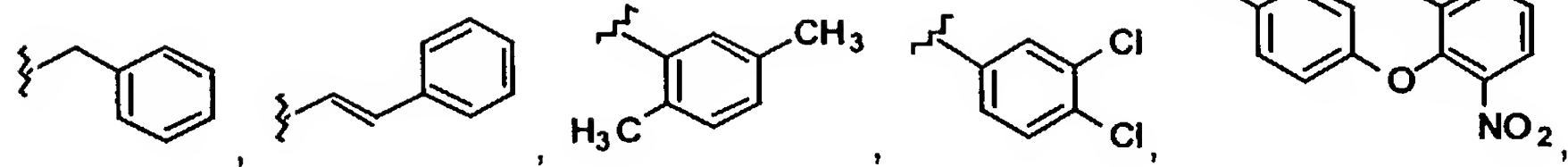
, where  $R^{3e} =$



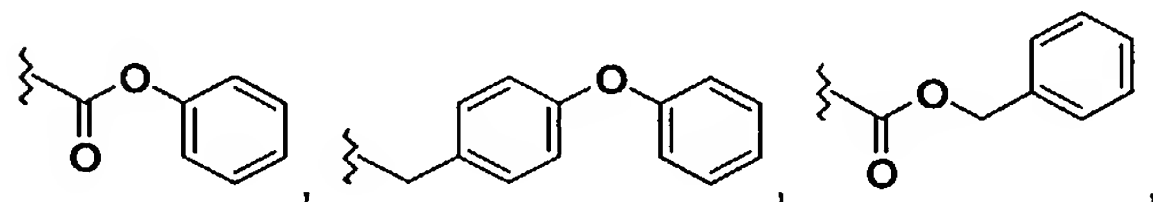
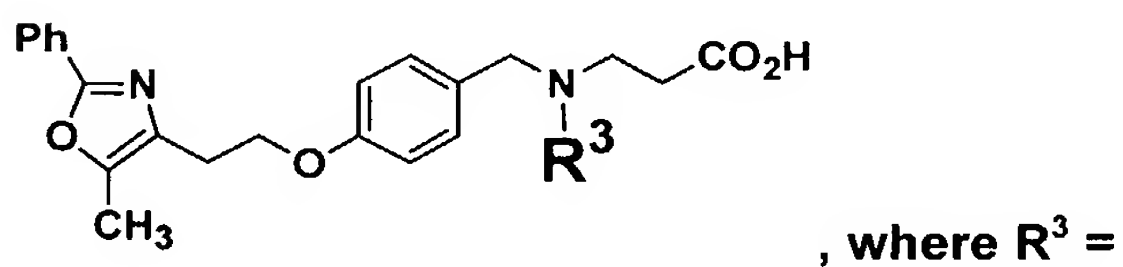
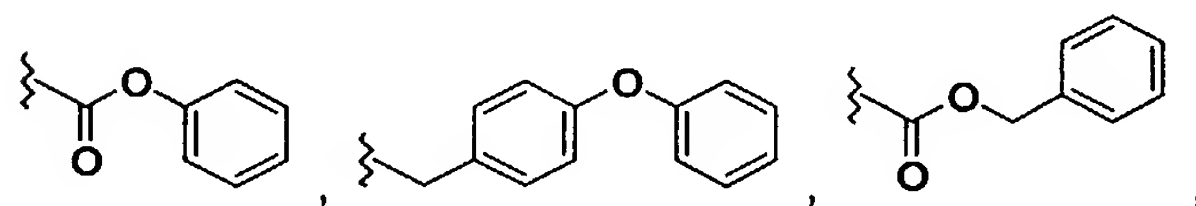
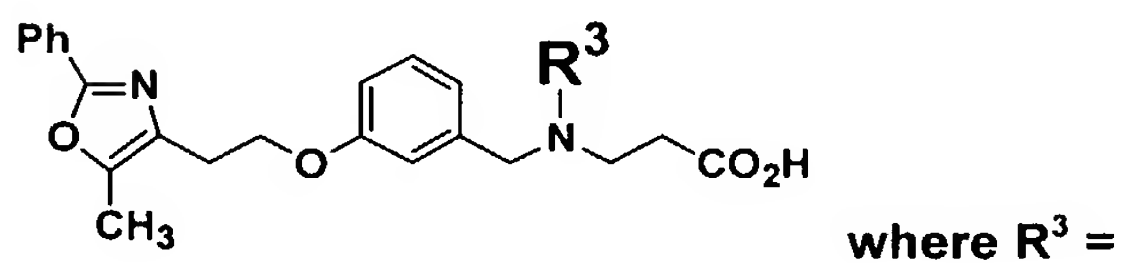
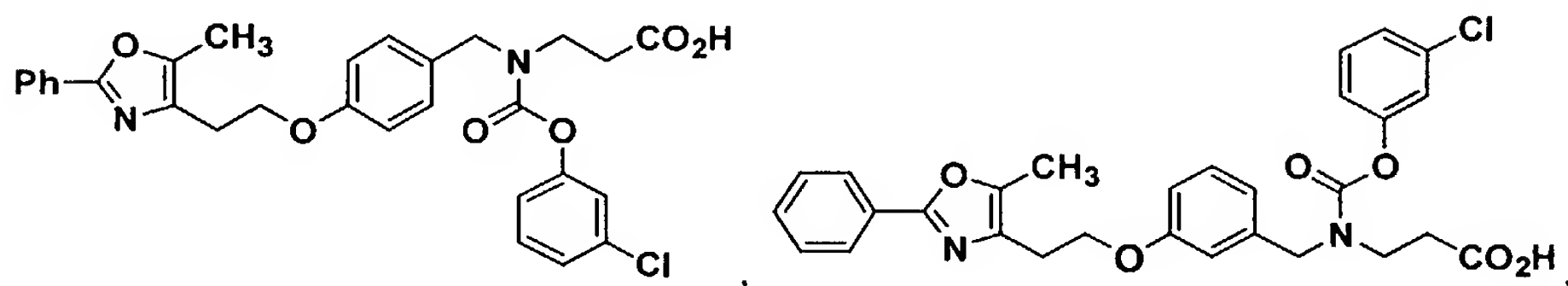
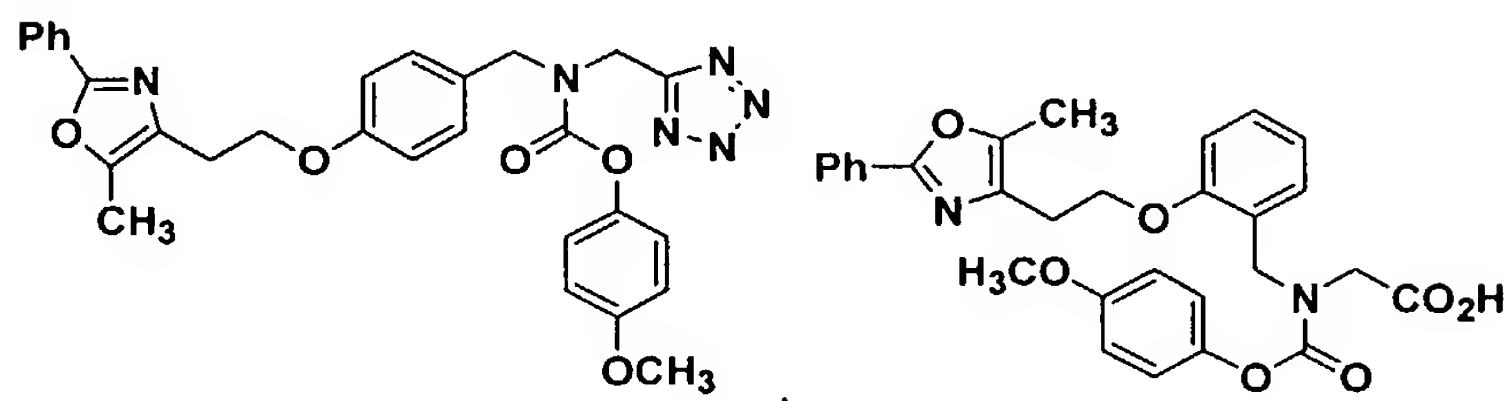
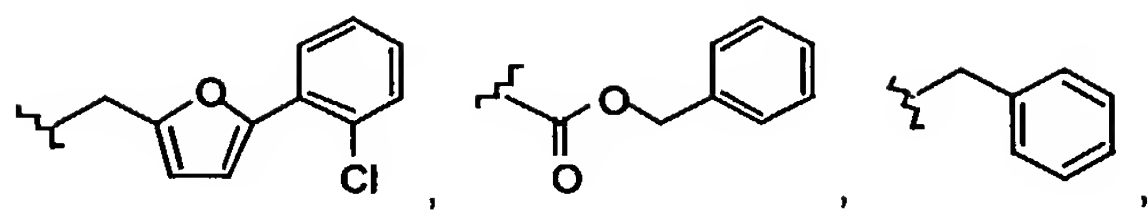


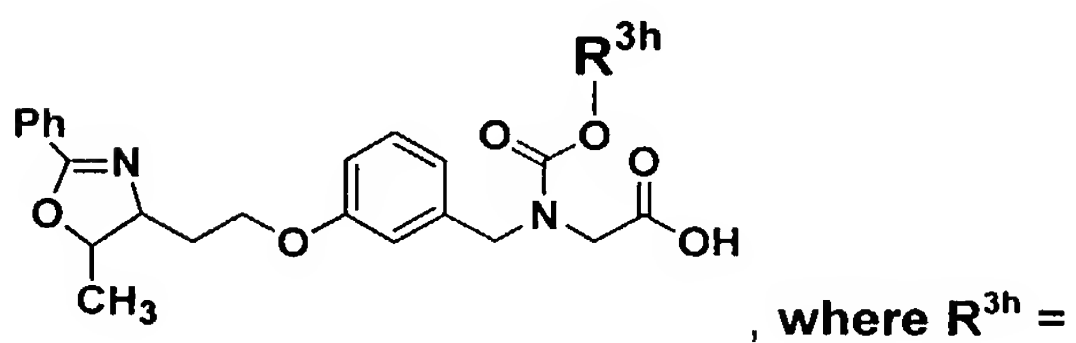
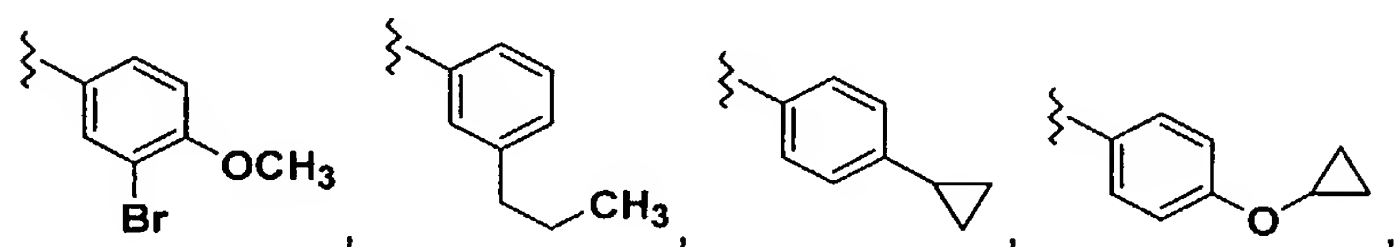
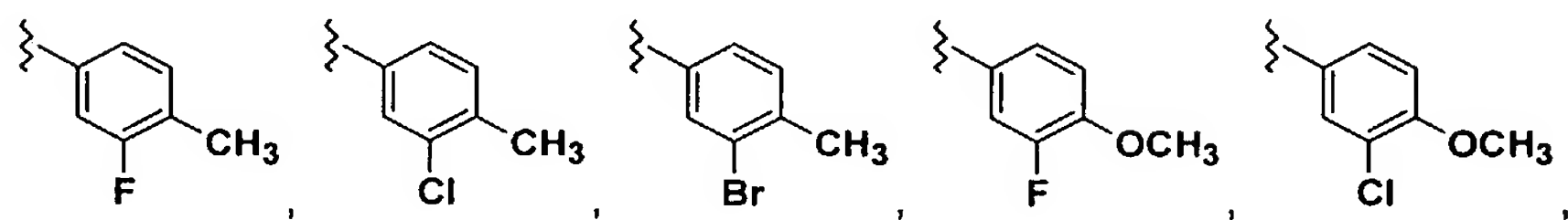
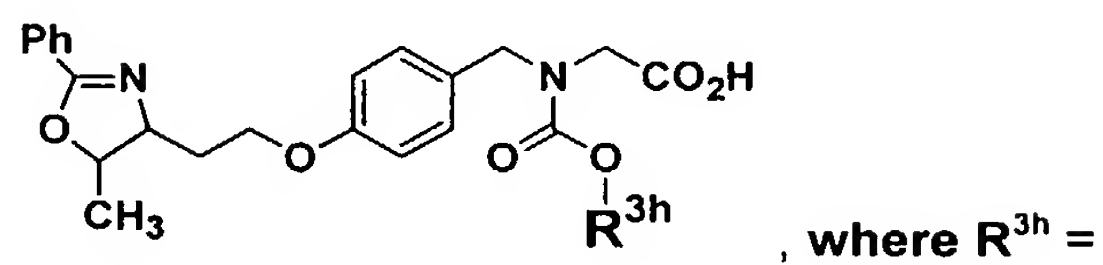
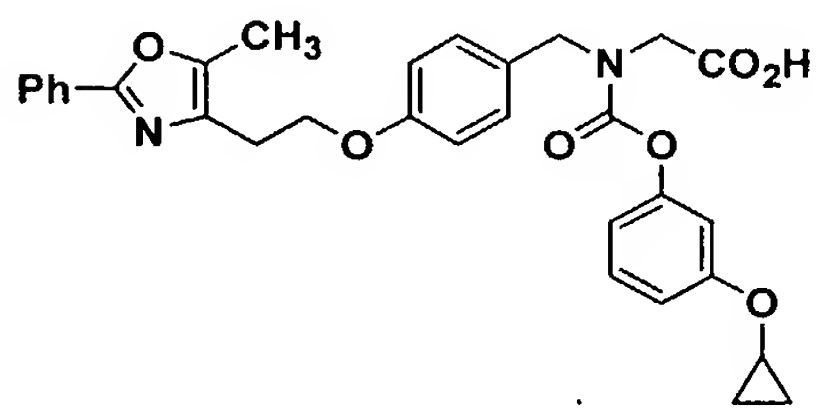
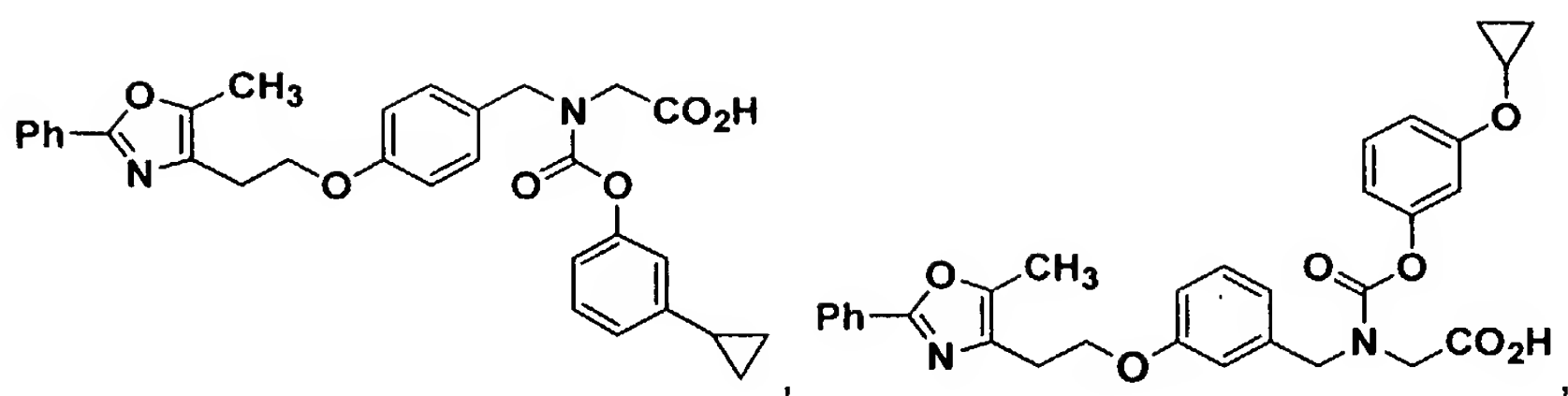




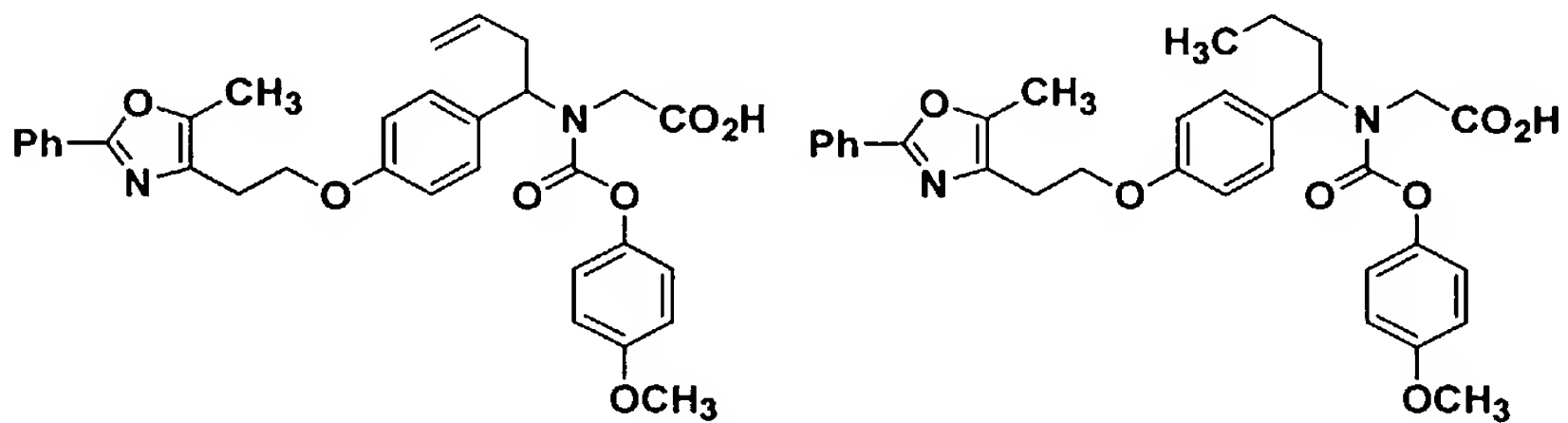
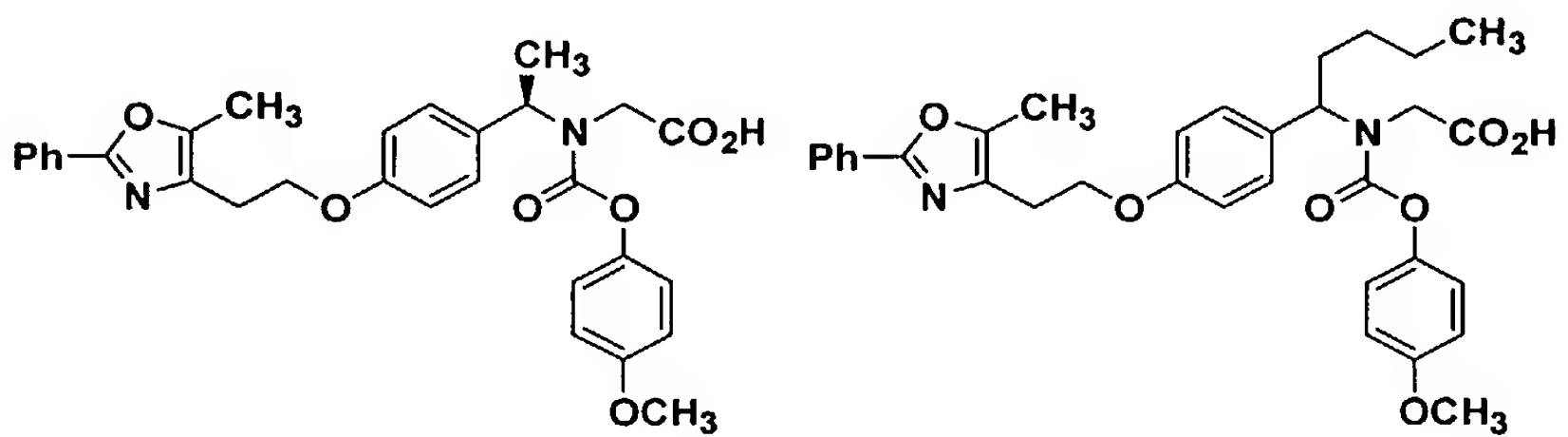
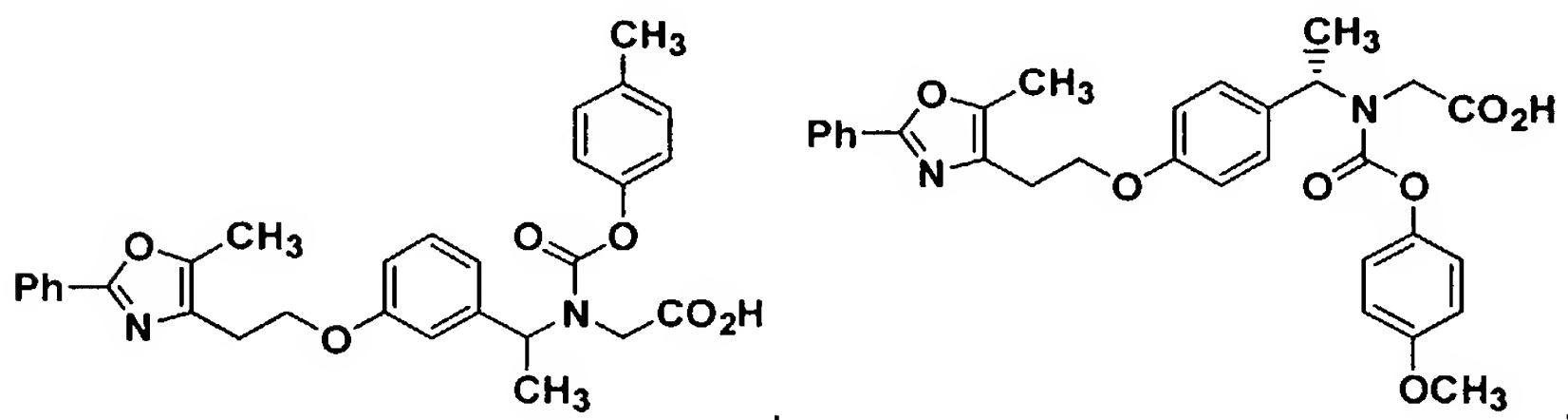
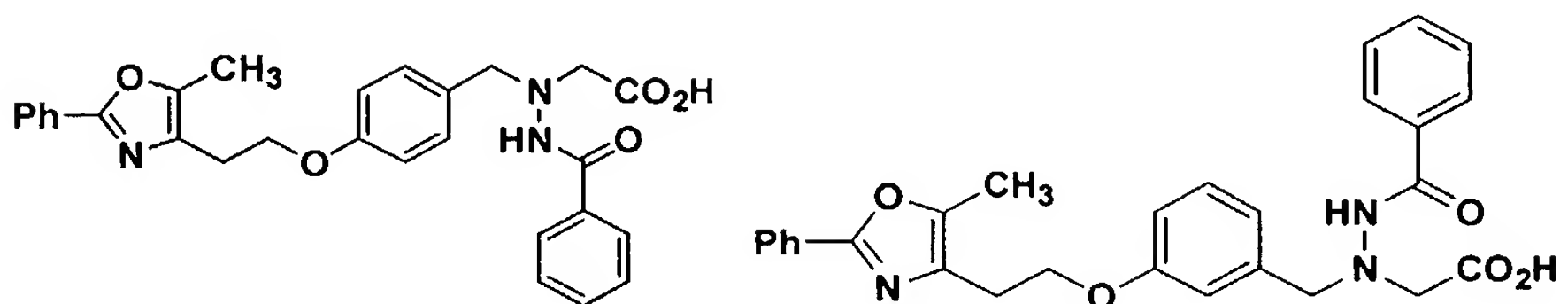
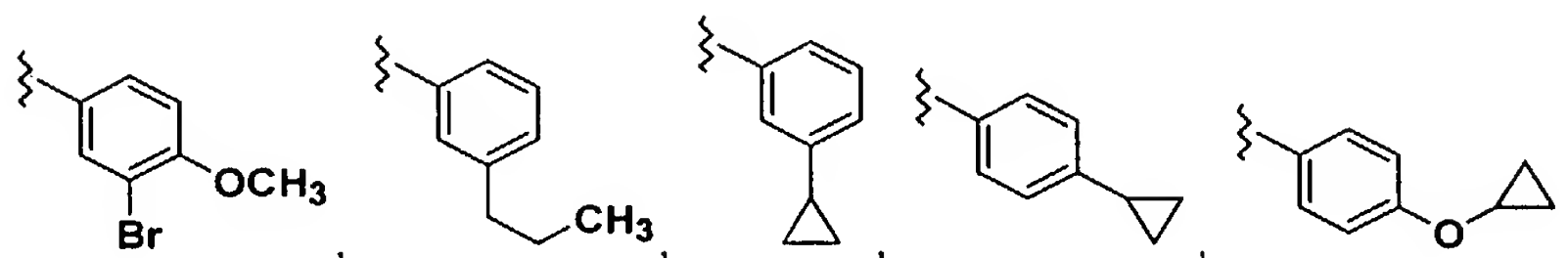
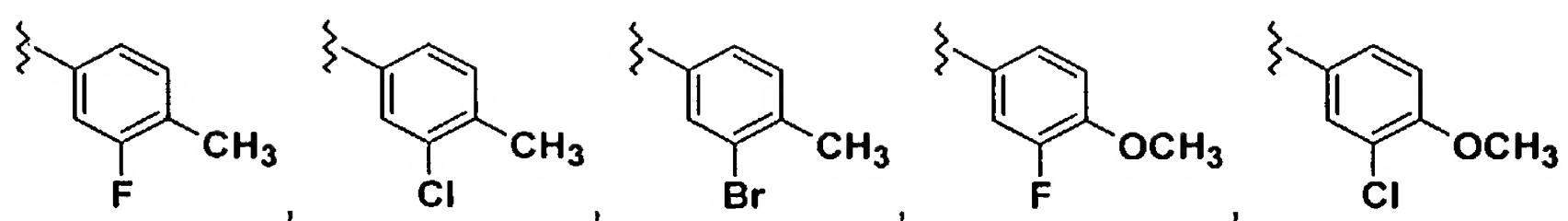


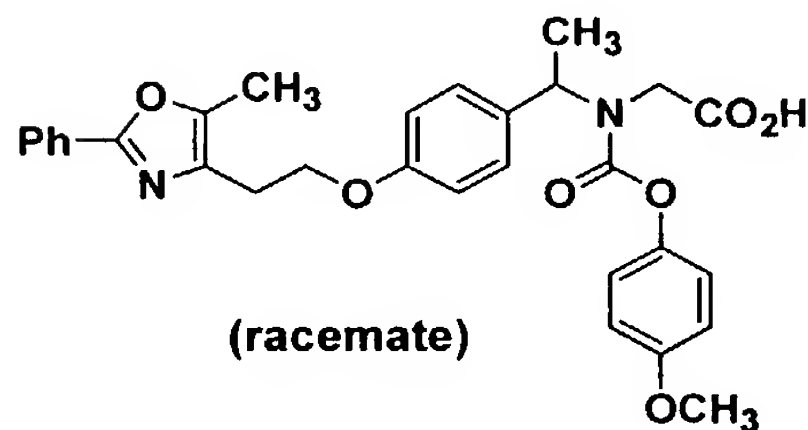
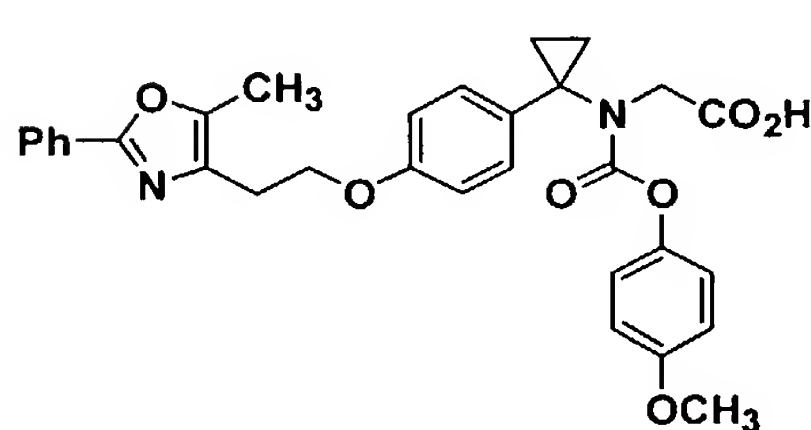
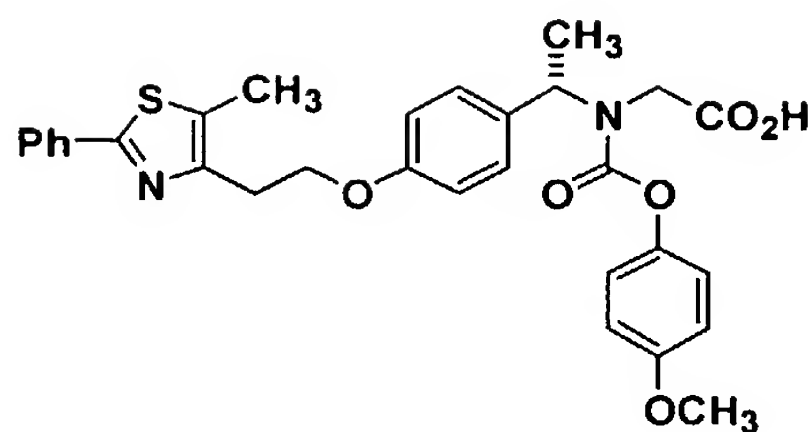
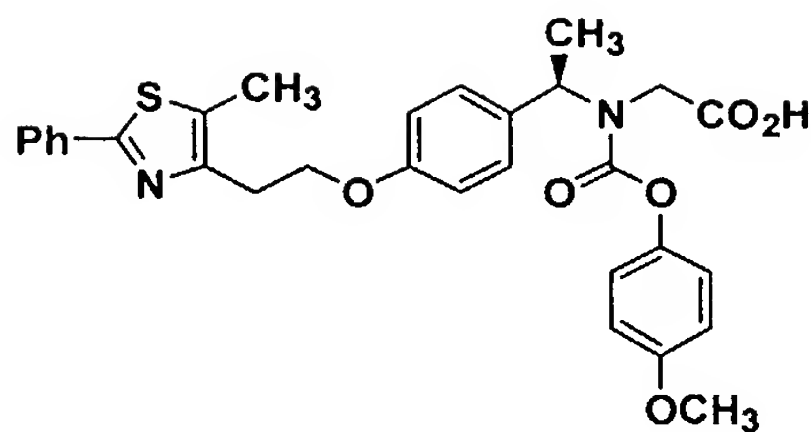
, where  $R^3 =$



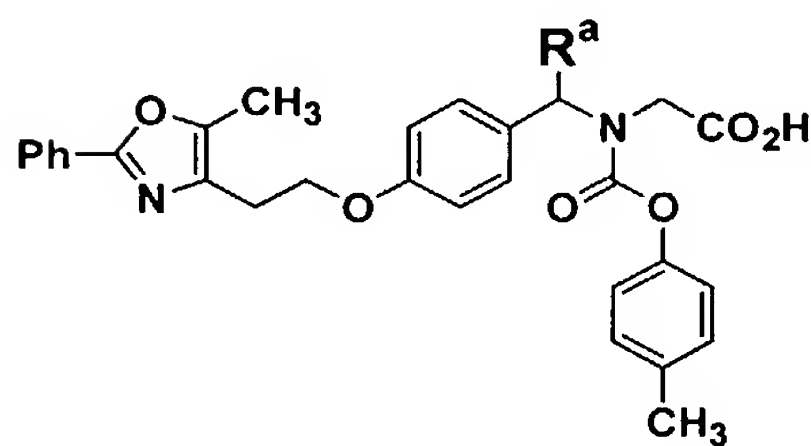




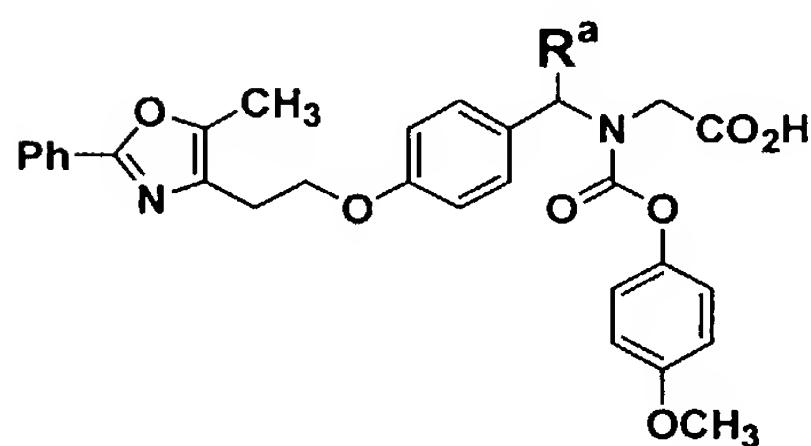




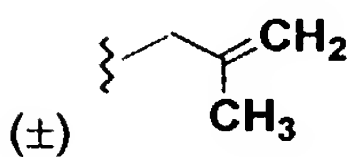
(racemate)

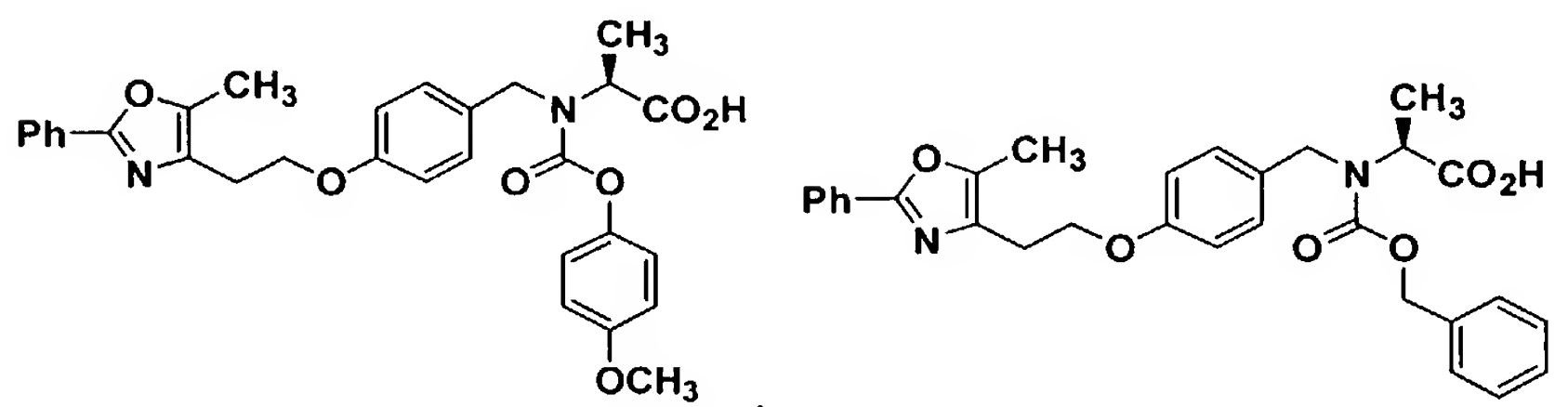
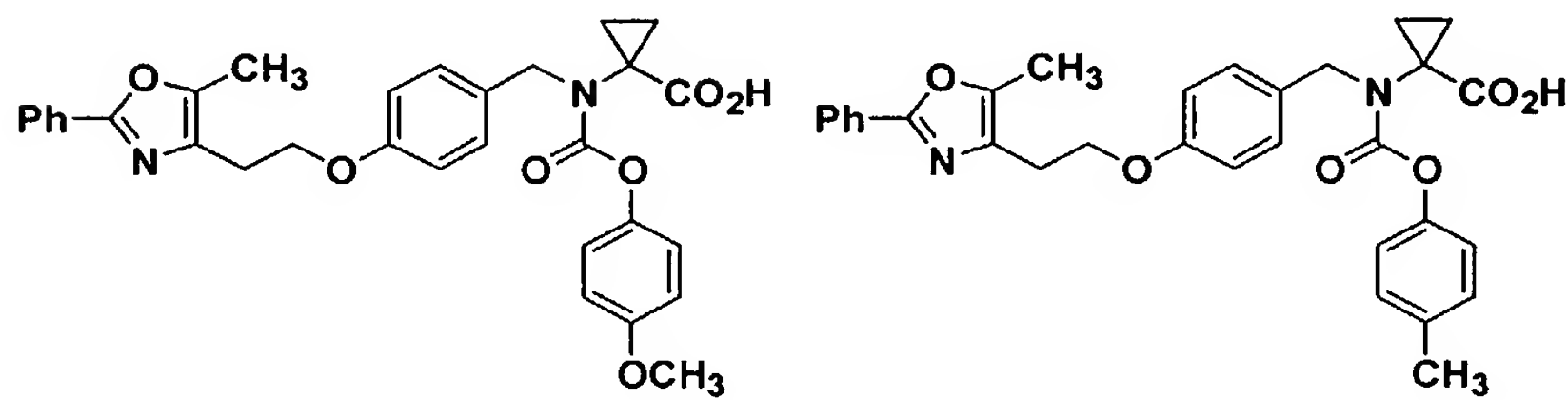
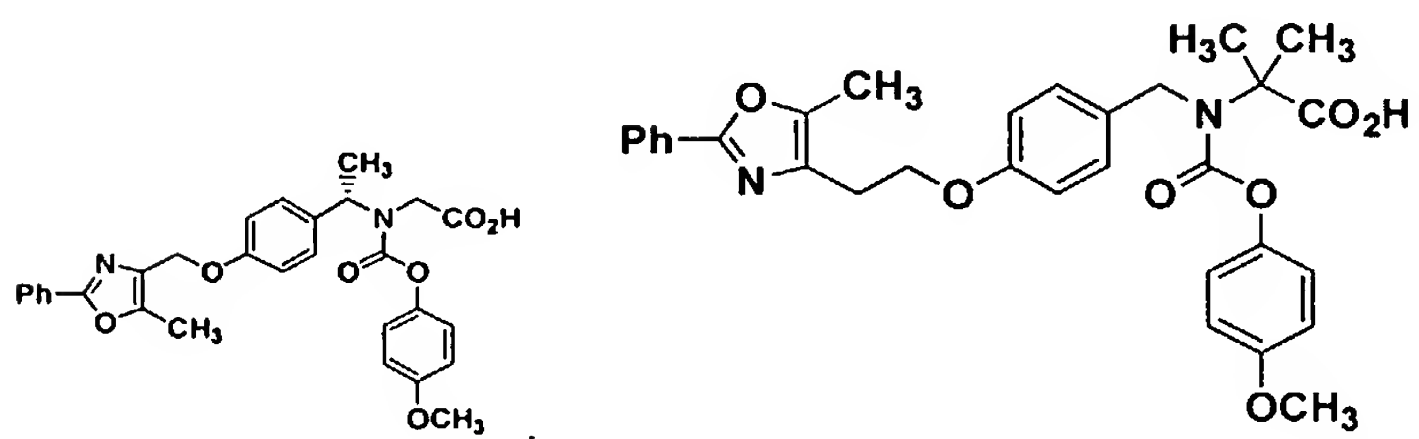
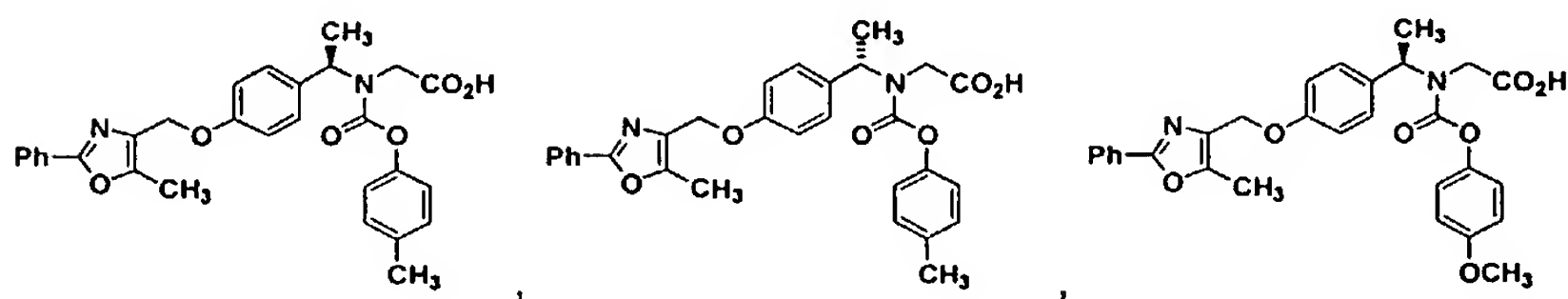
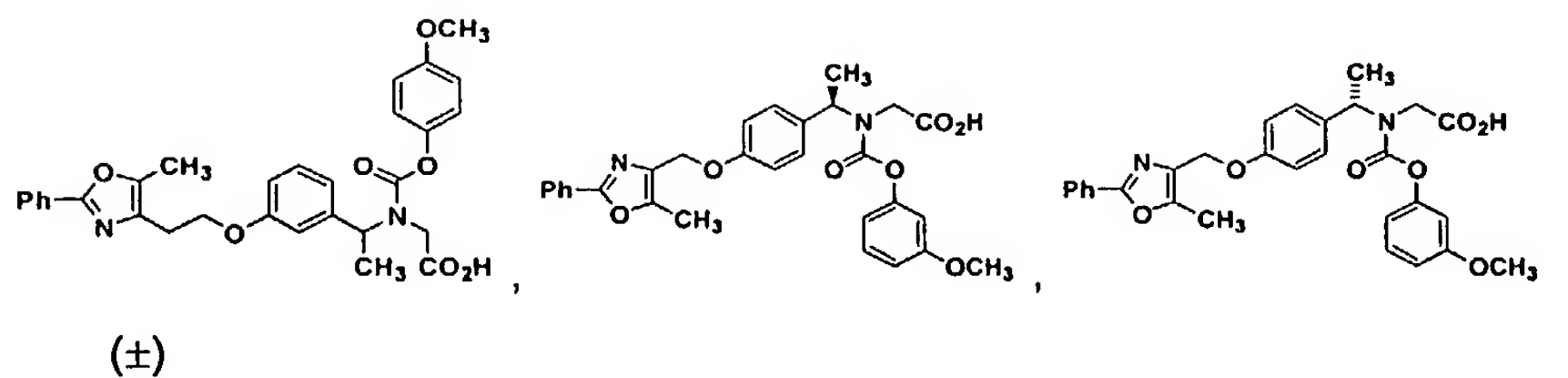


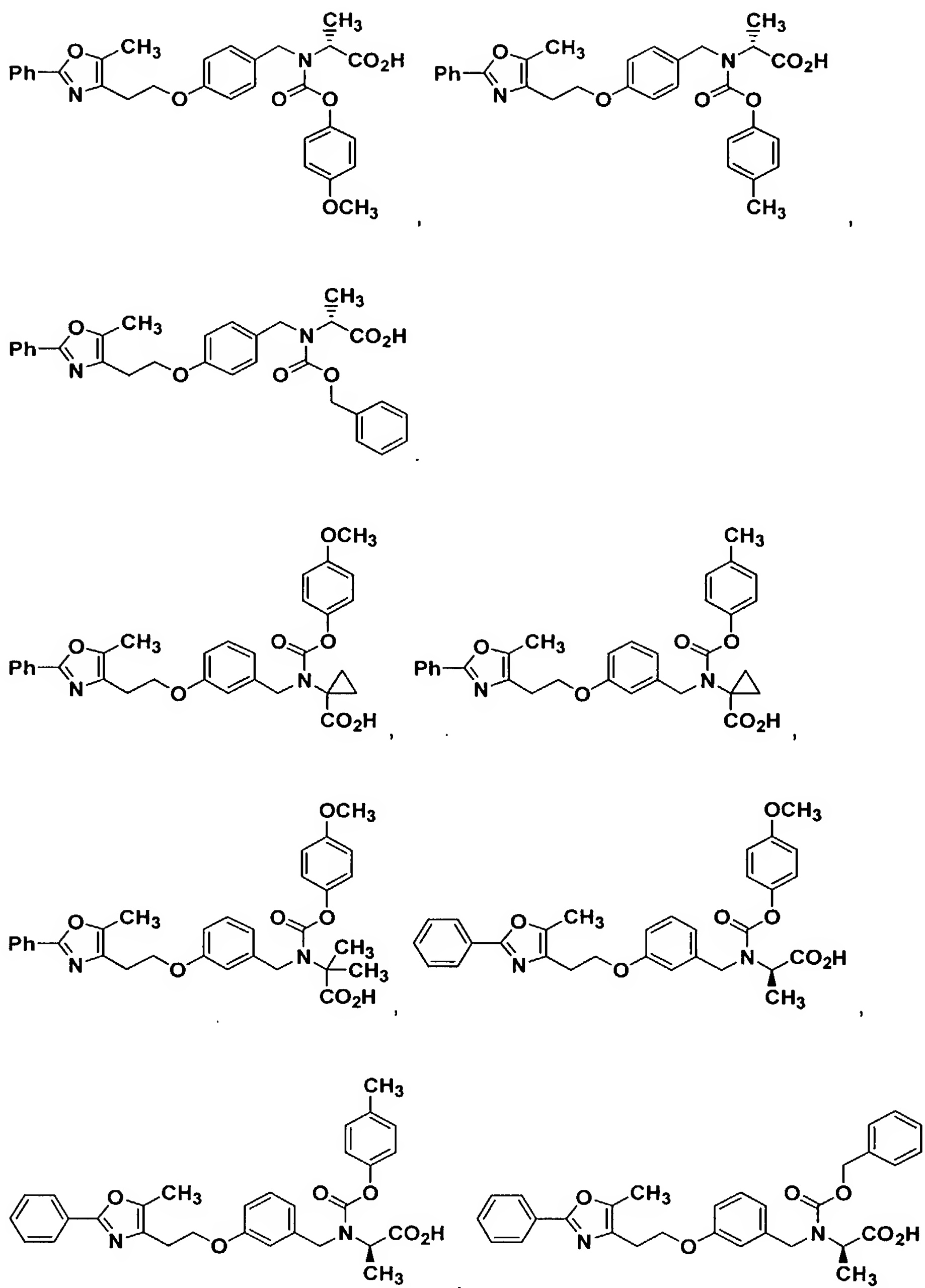
, where R<sup>a</sup> = (±)-Me, (±) n-Bu,

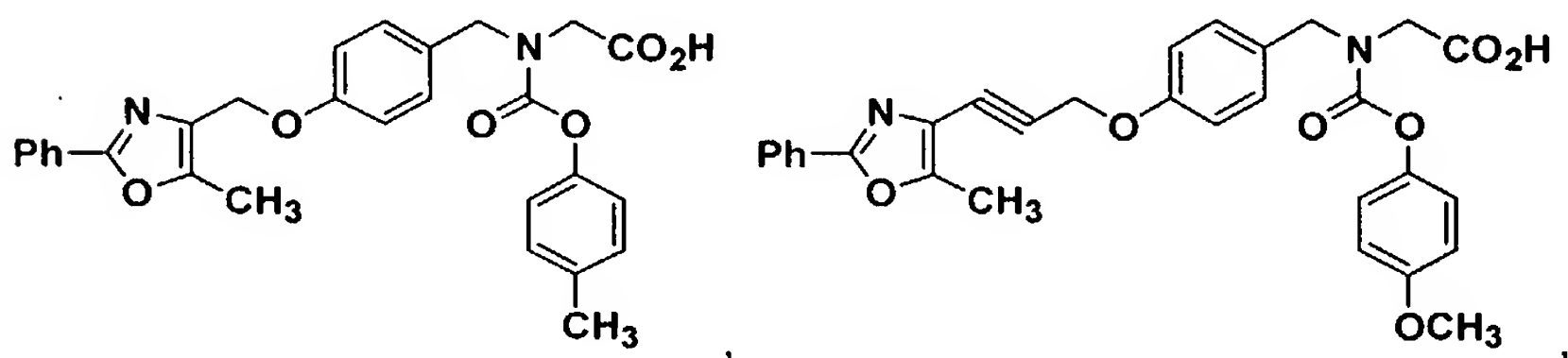
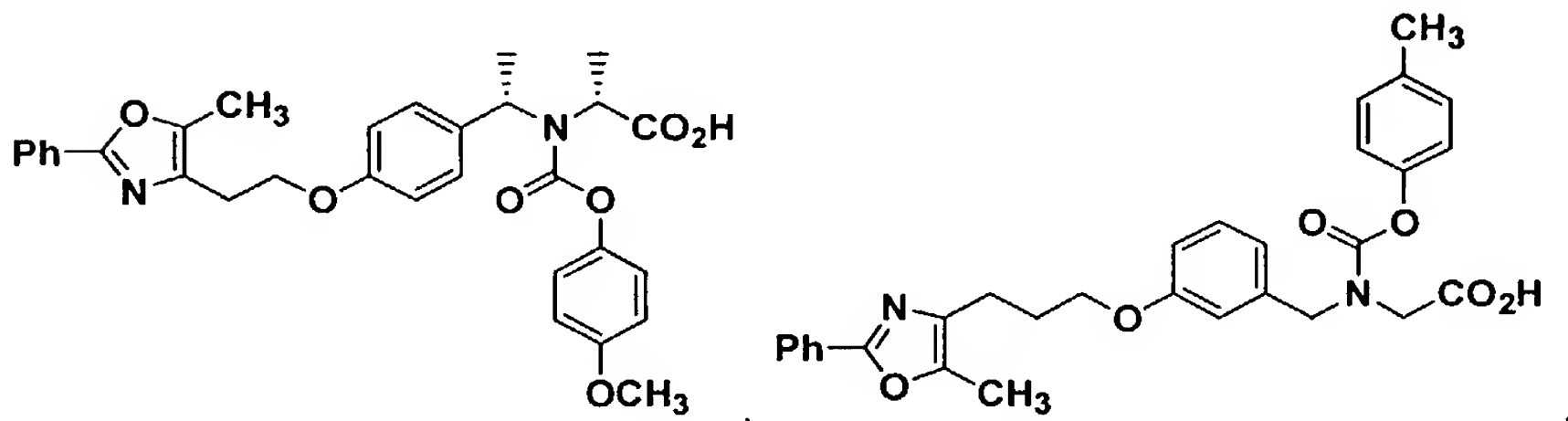
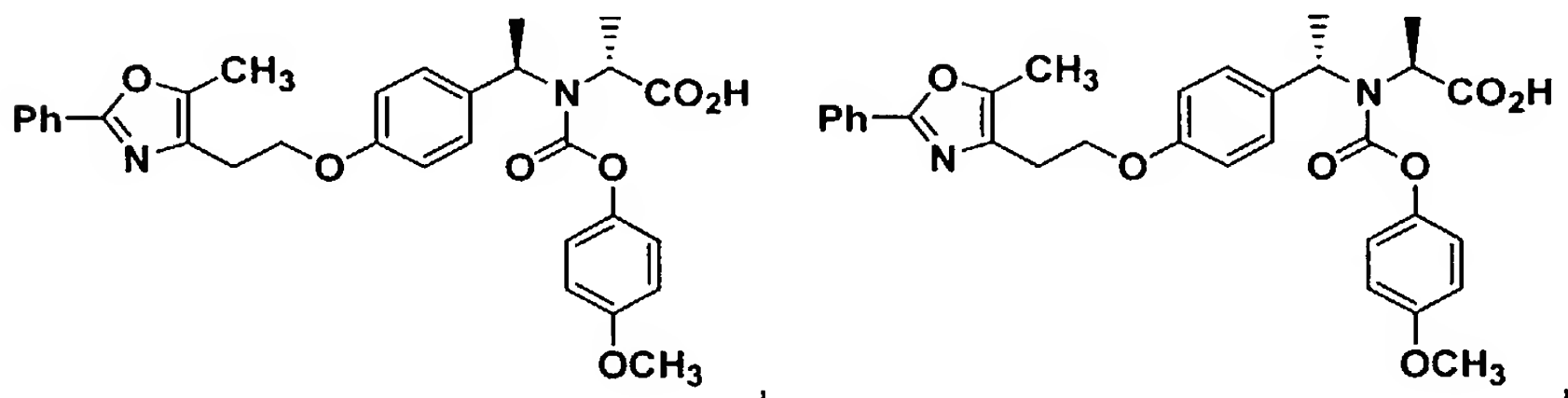
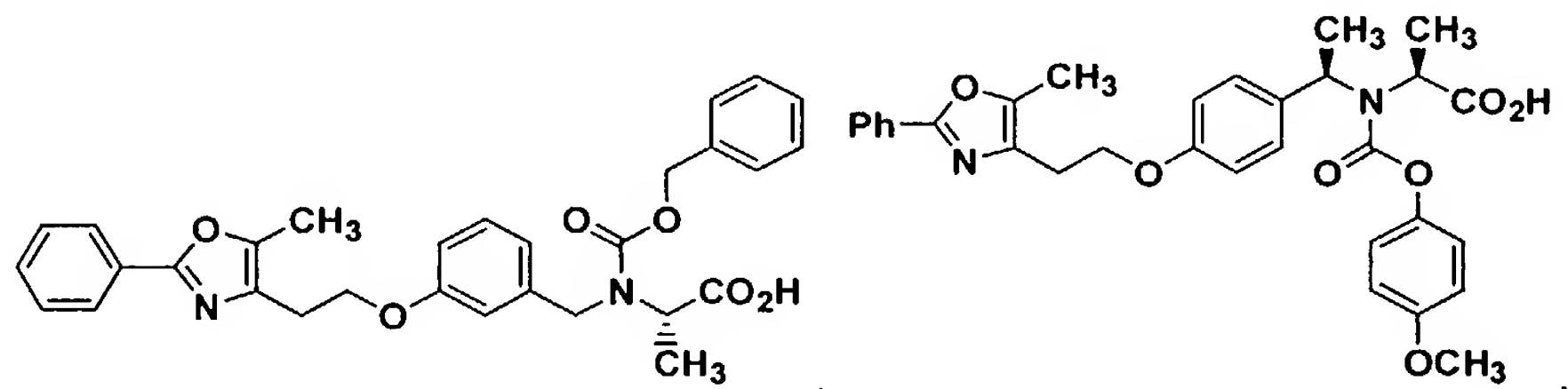
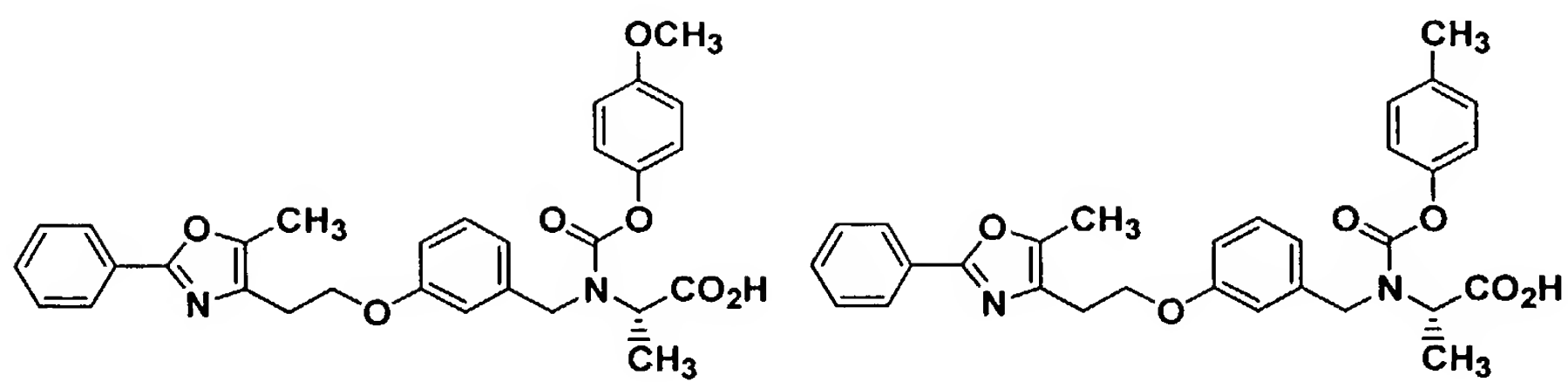


, where R<sup>a</sup> = (±) Et, (±) i-Bu,

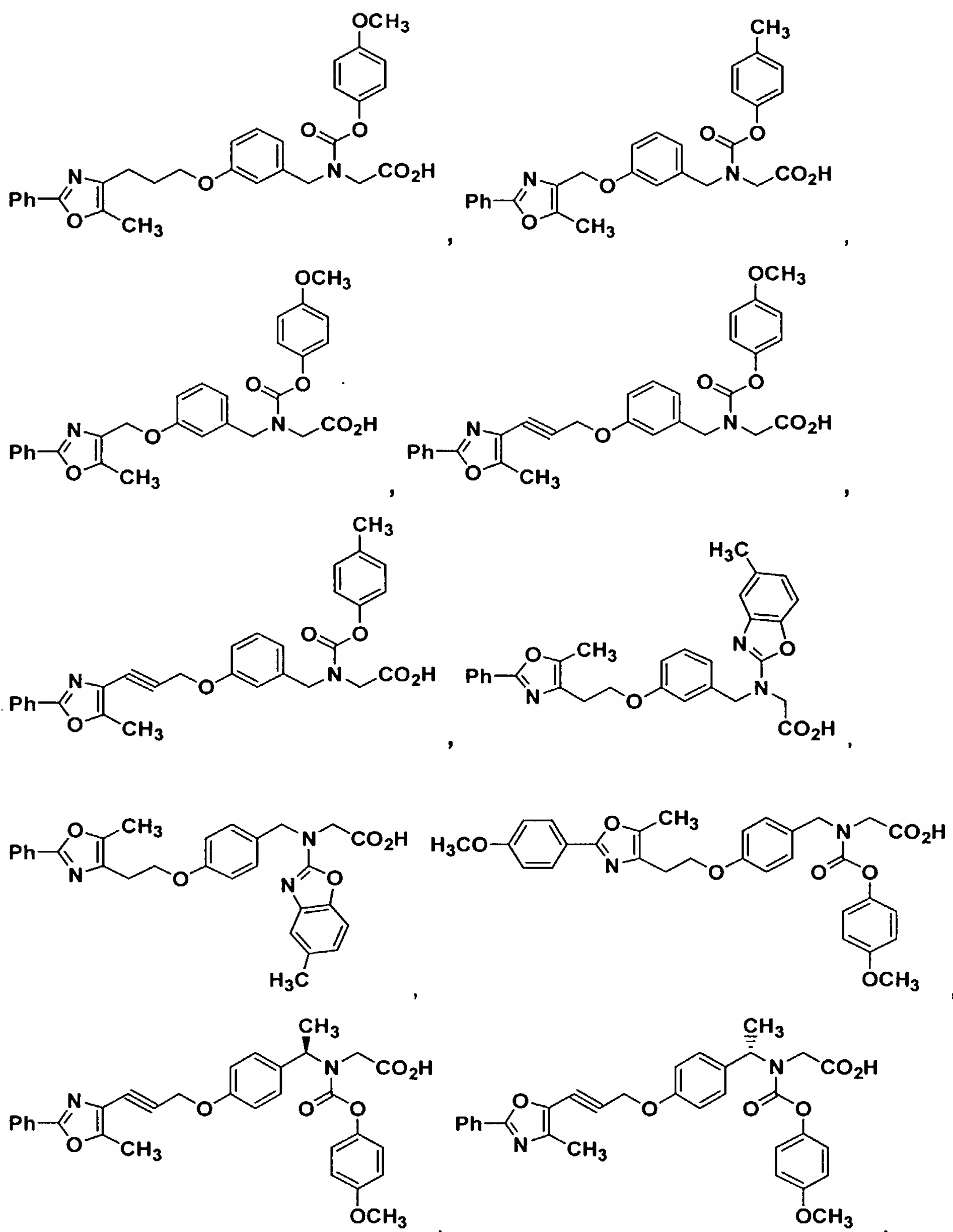


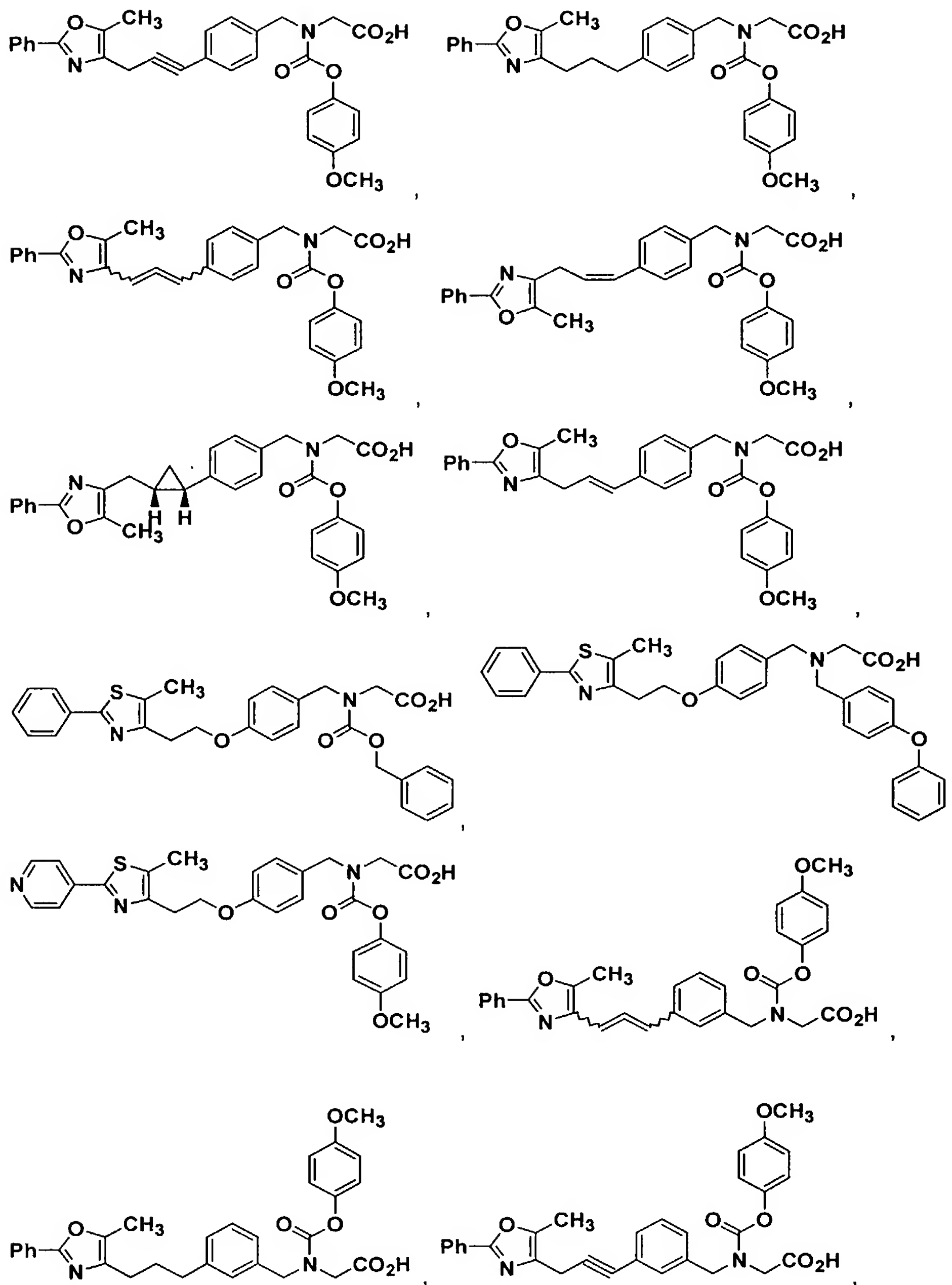




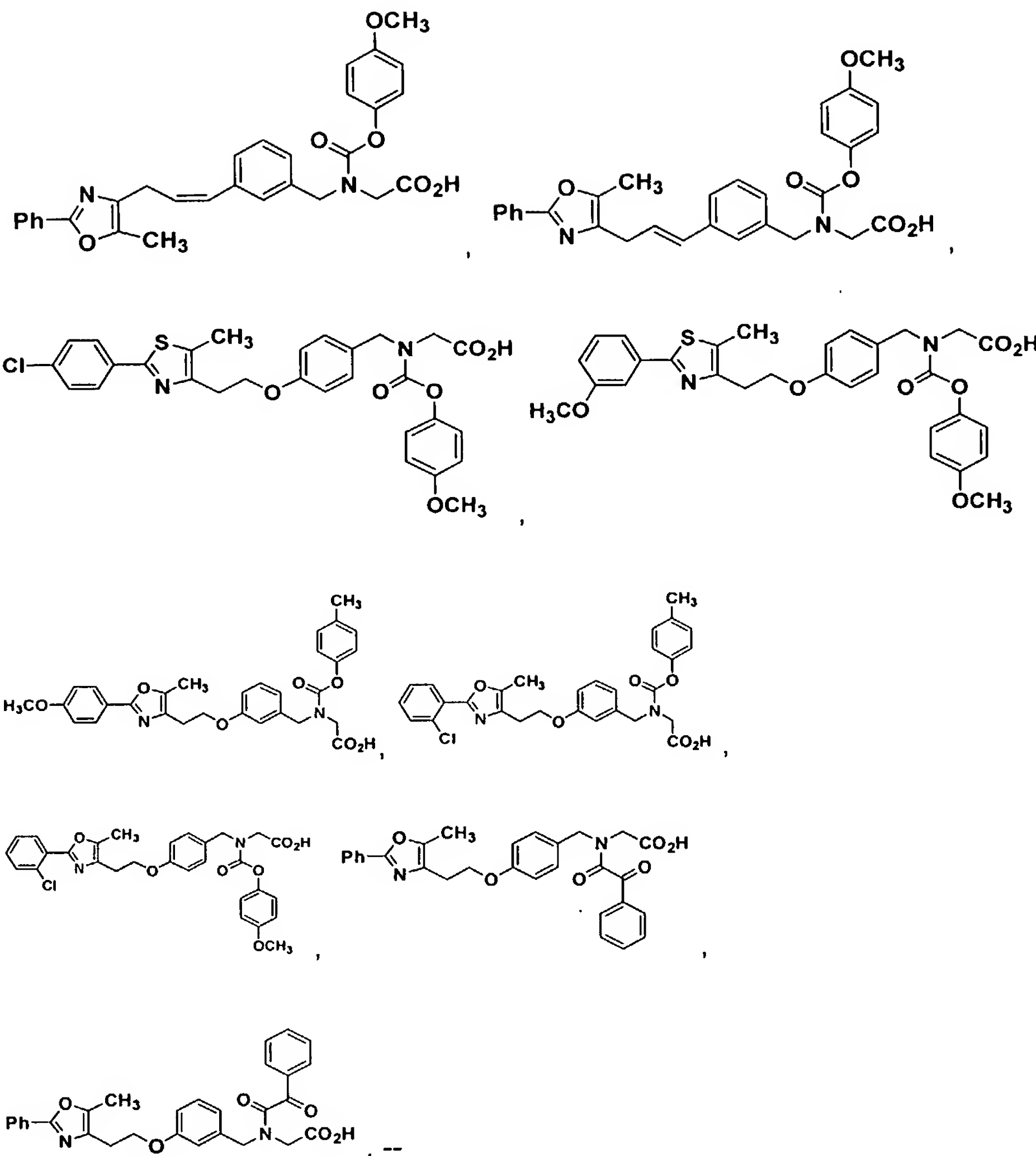






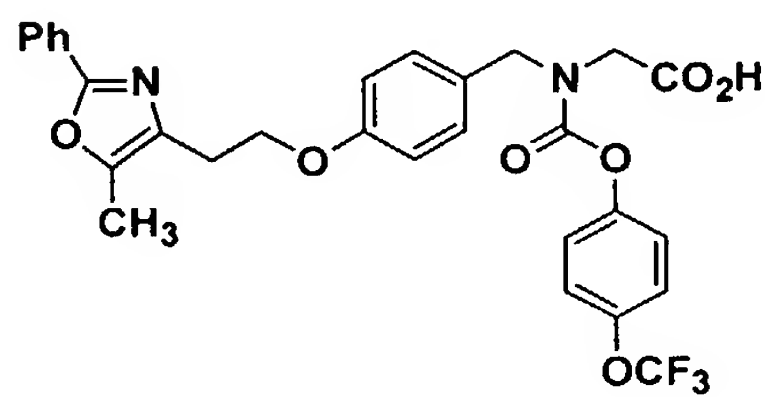
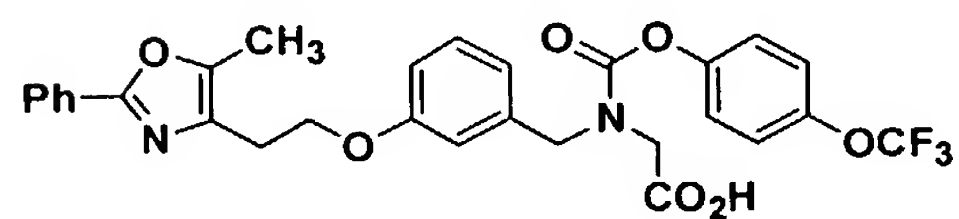
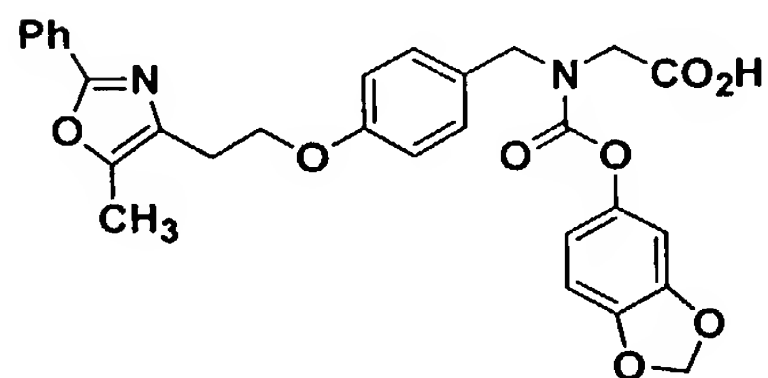
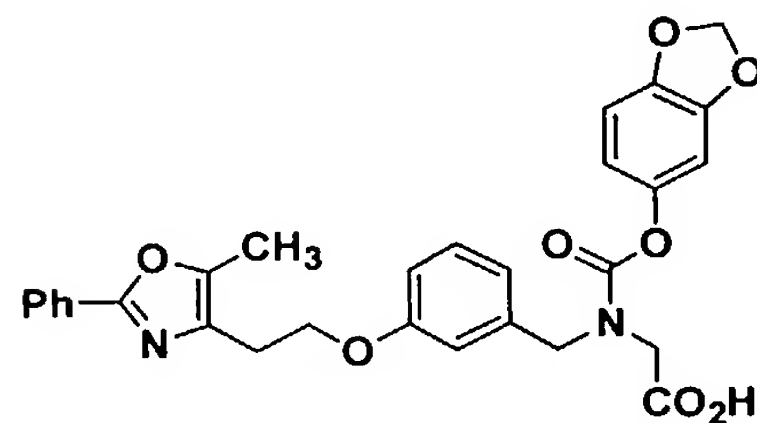
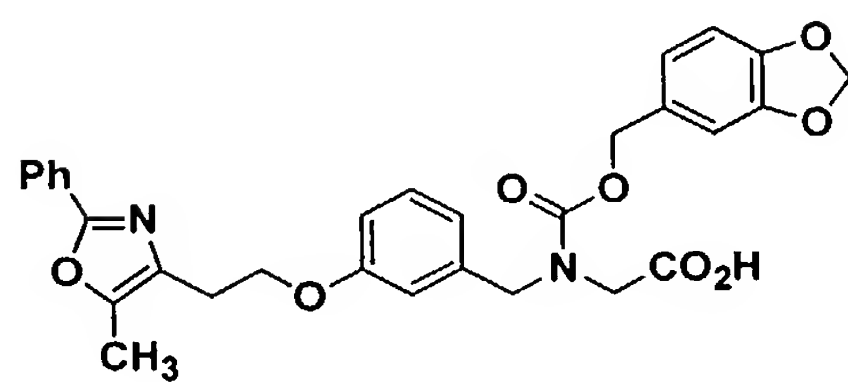
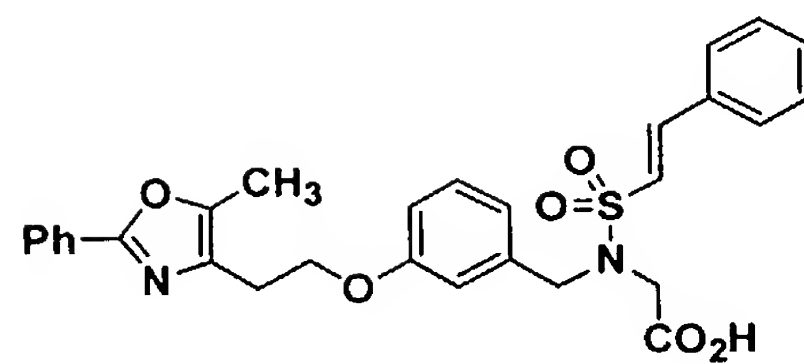
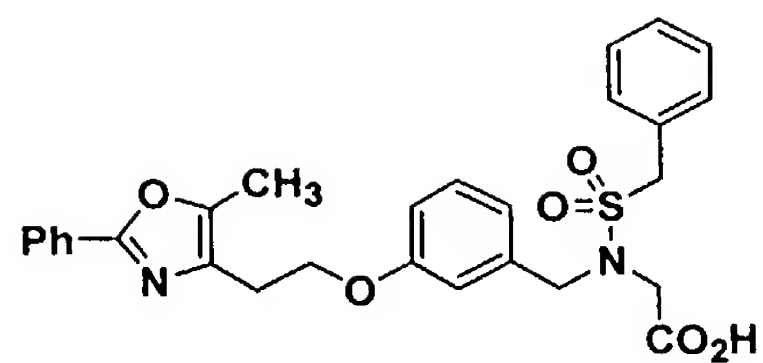


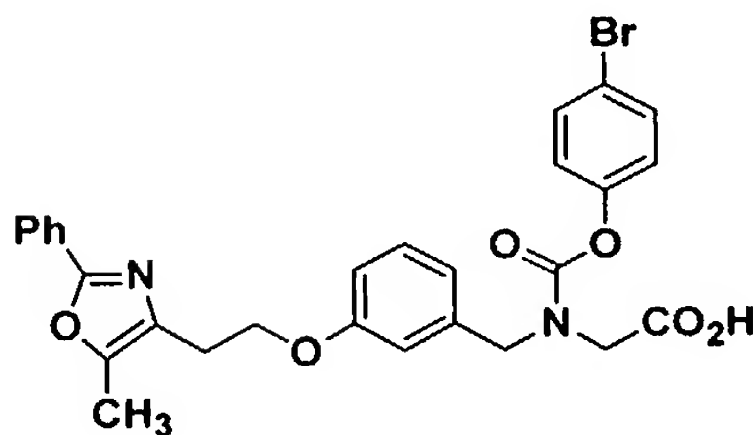
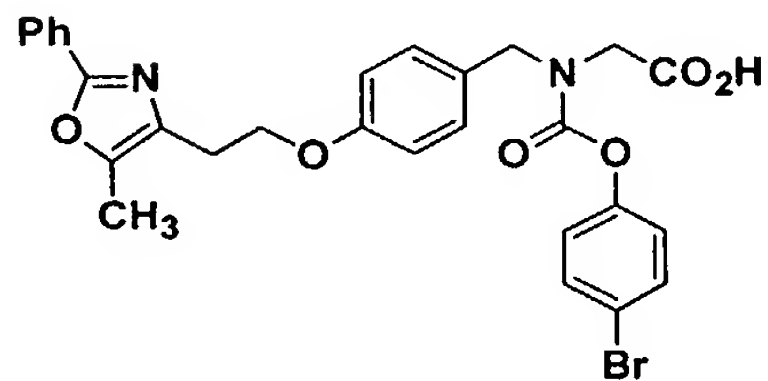
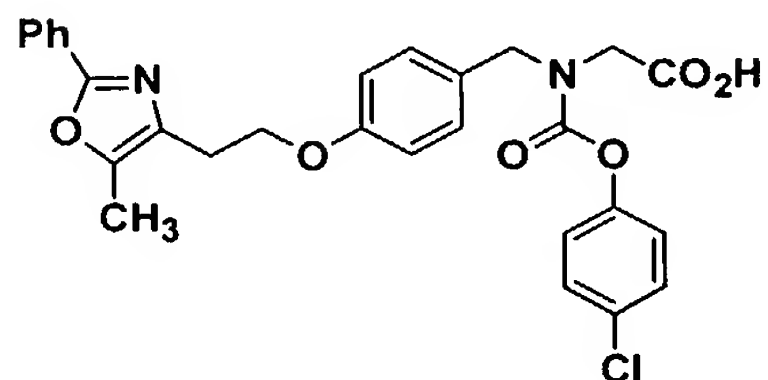
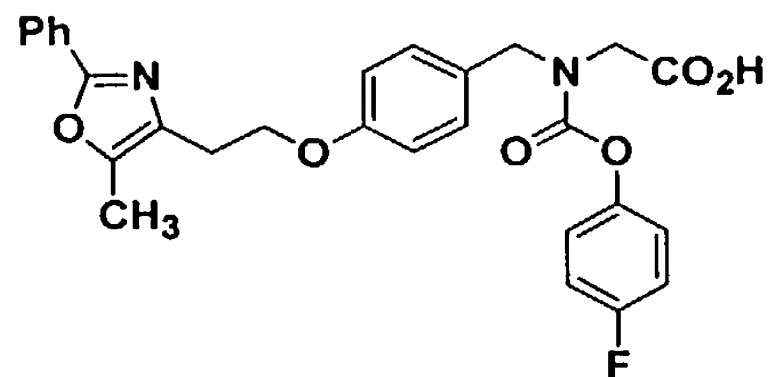
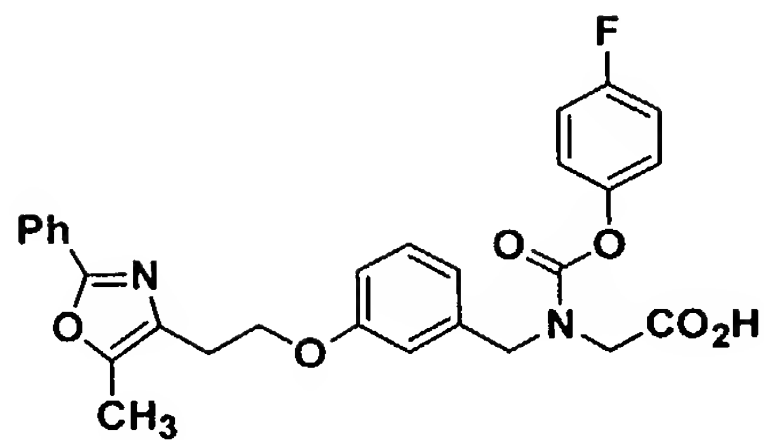
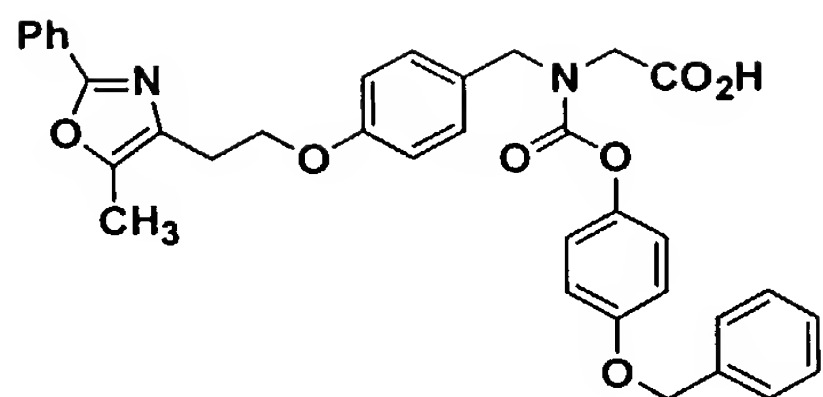


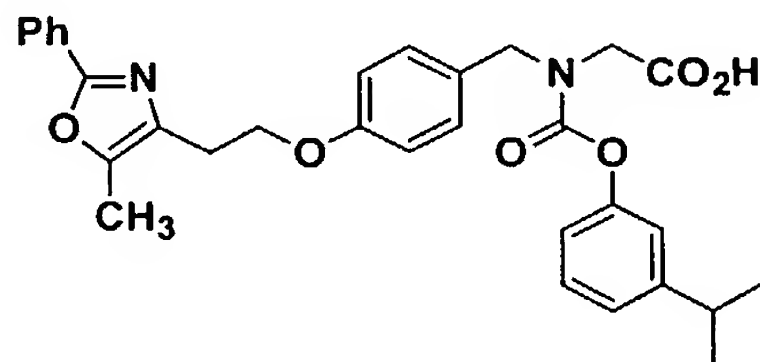
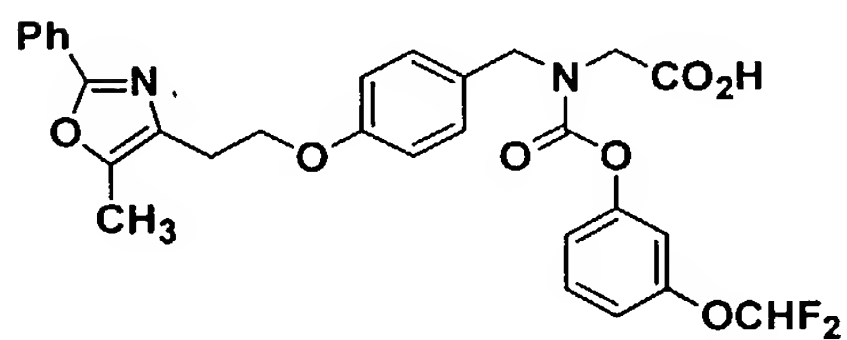
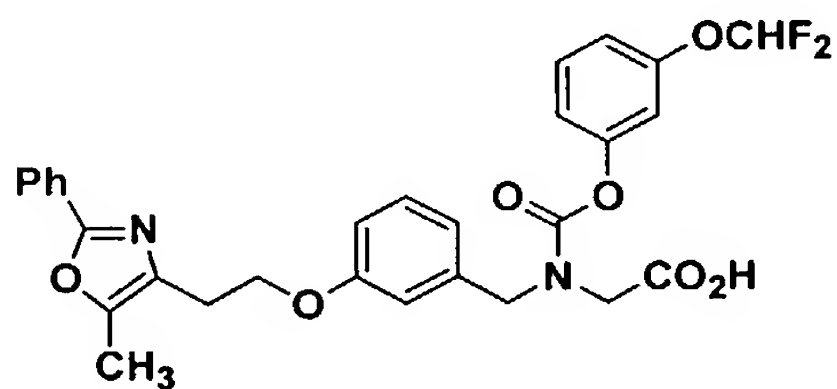
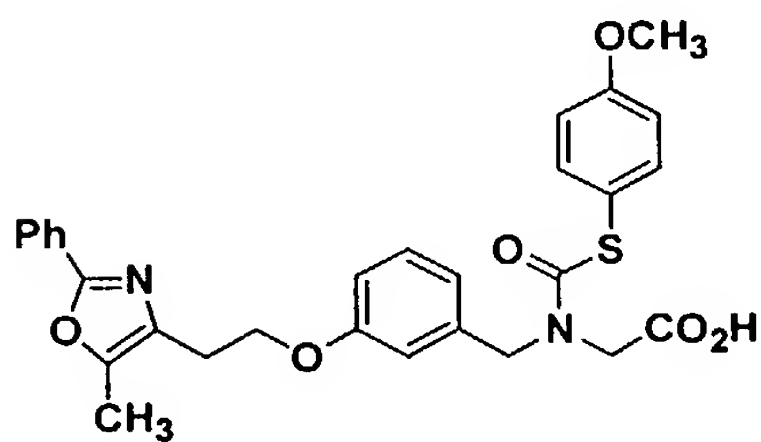
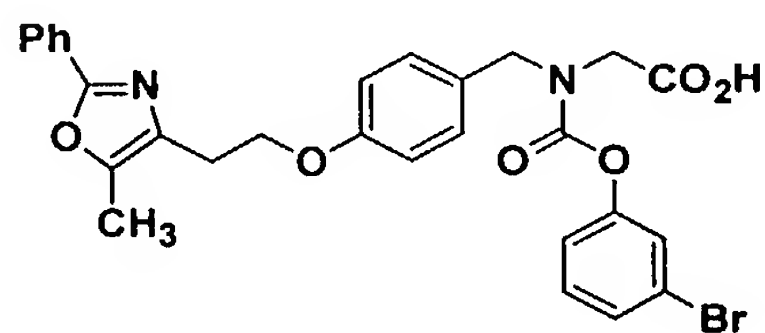
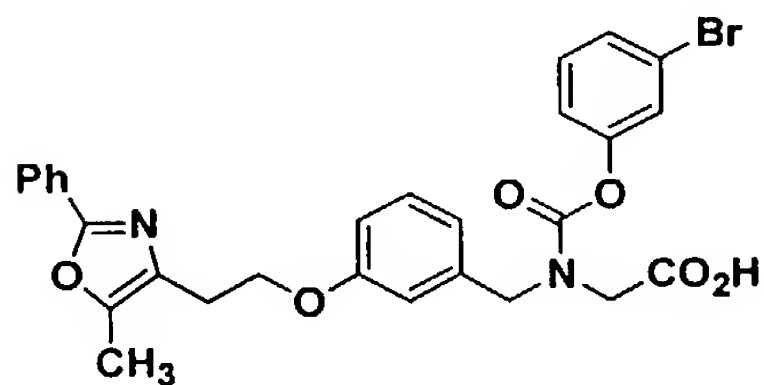
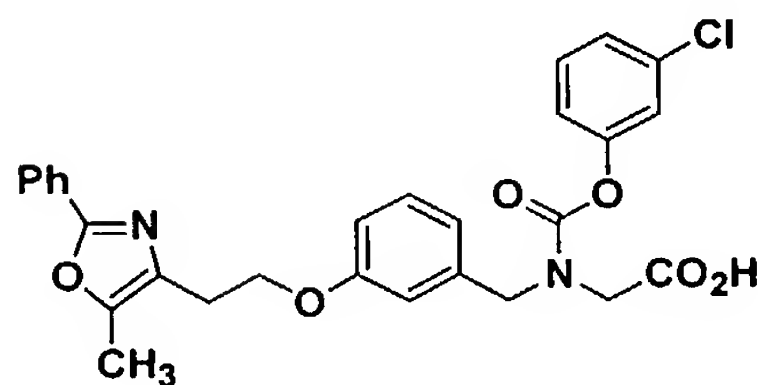
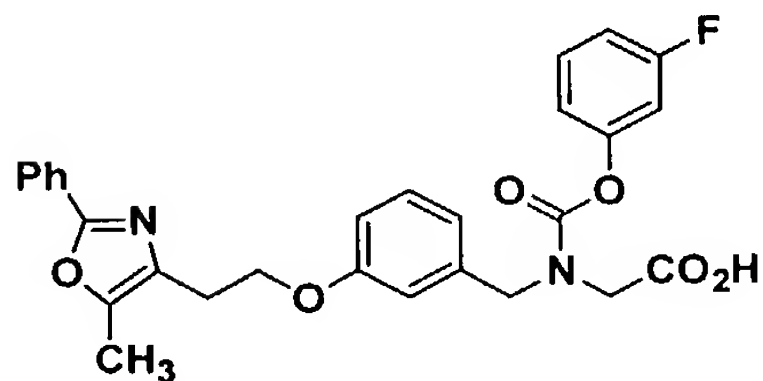
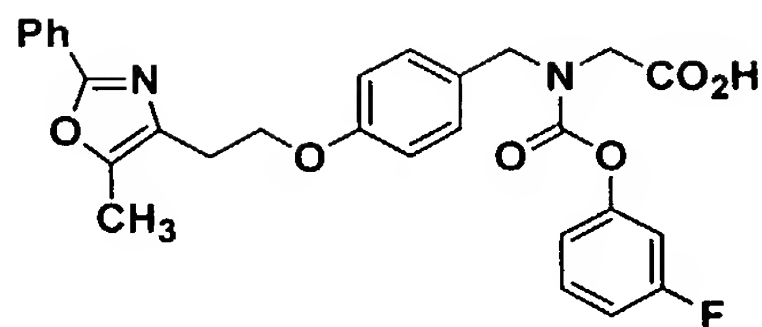
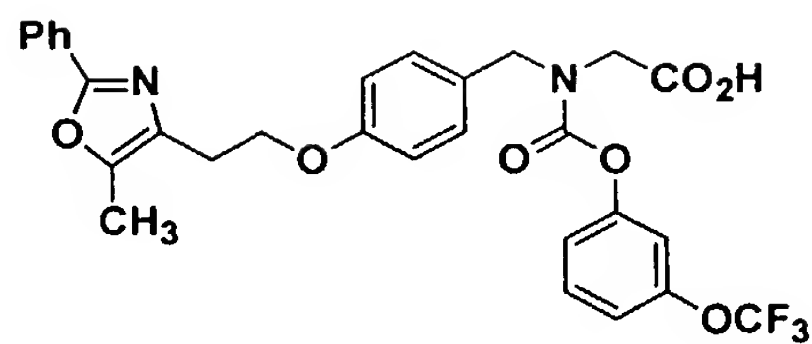


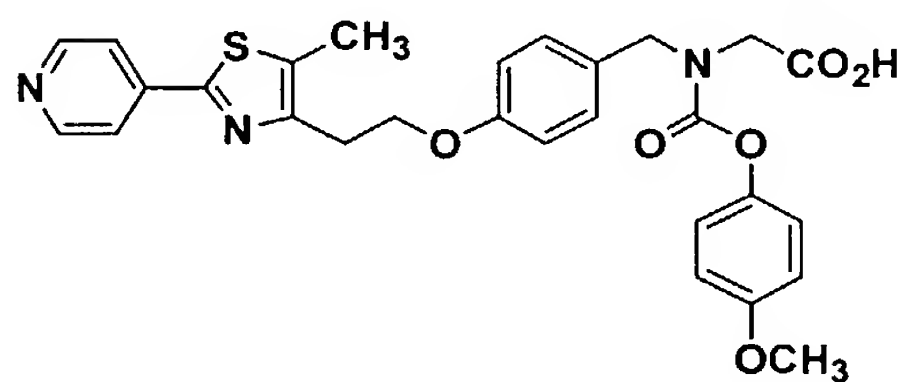
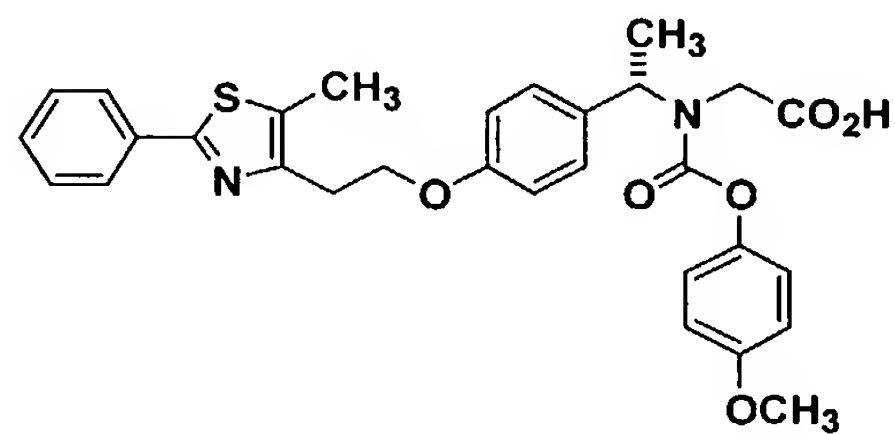
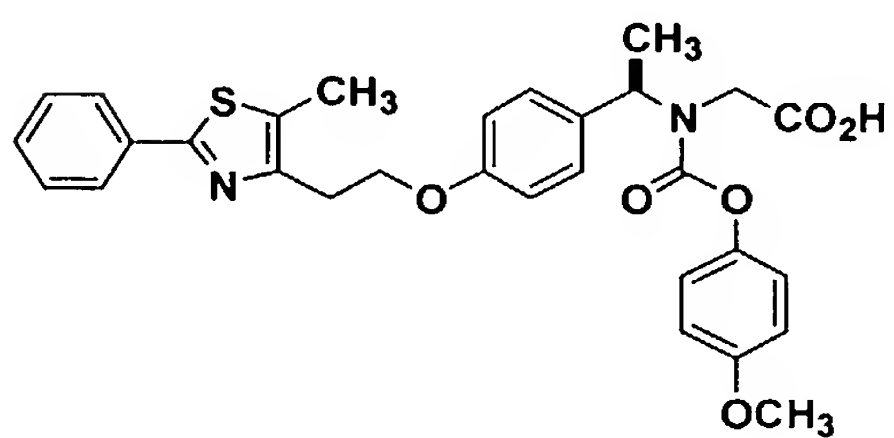
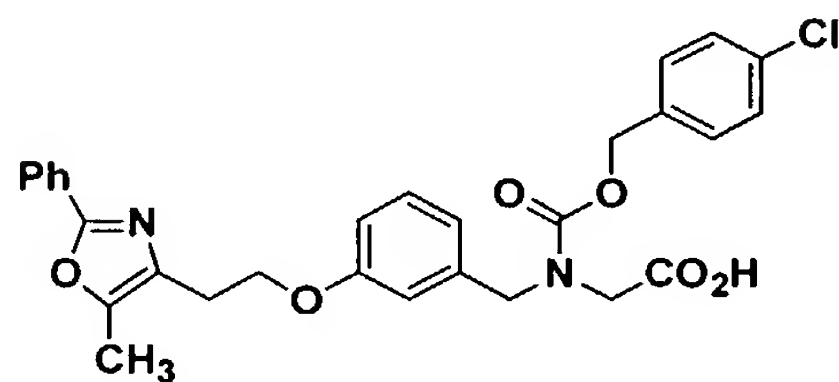
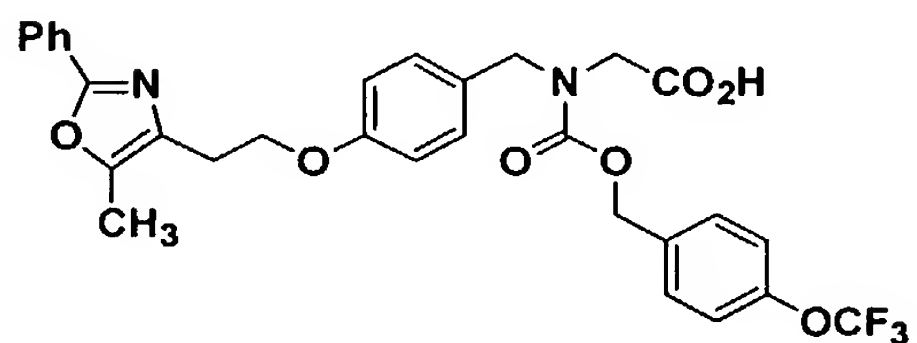
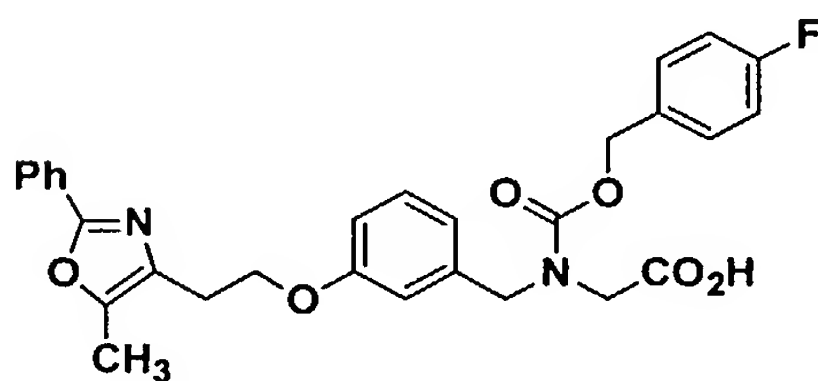
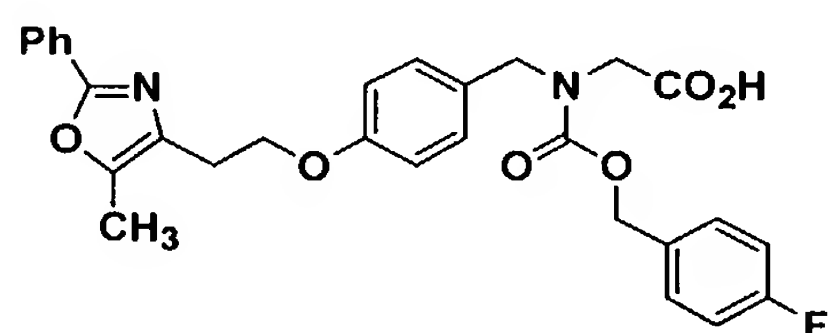
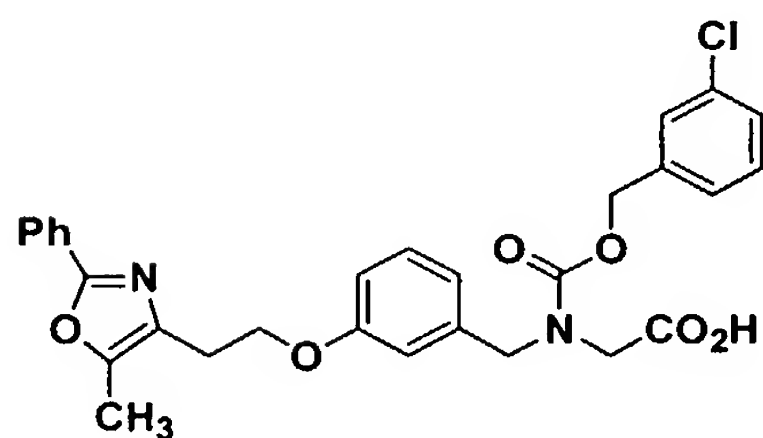
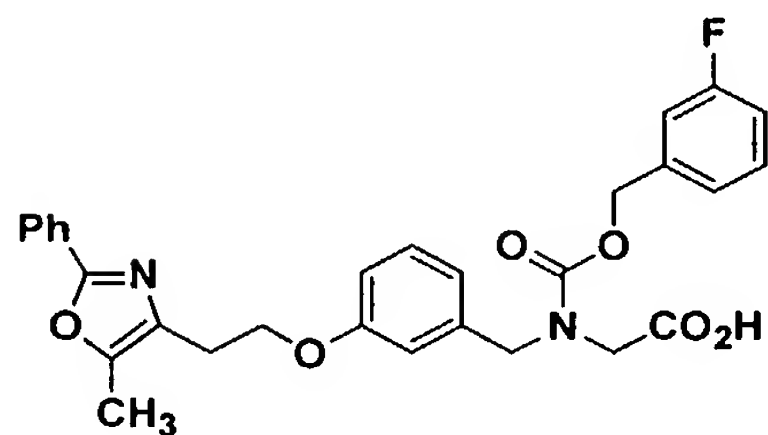
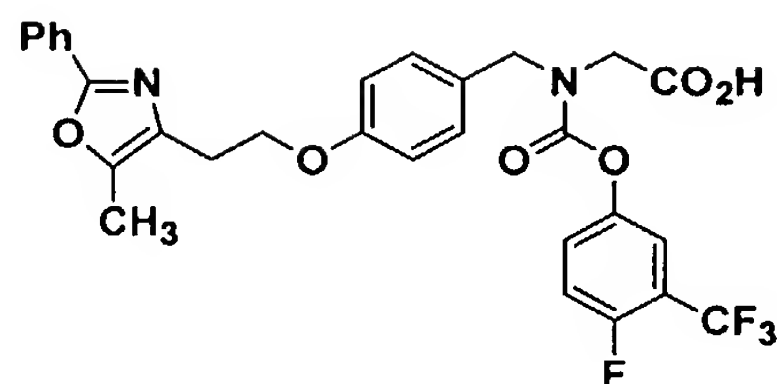
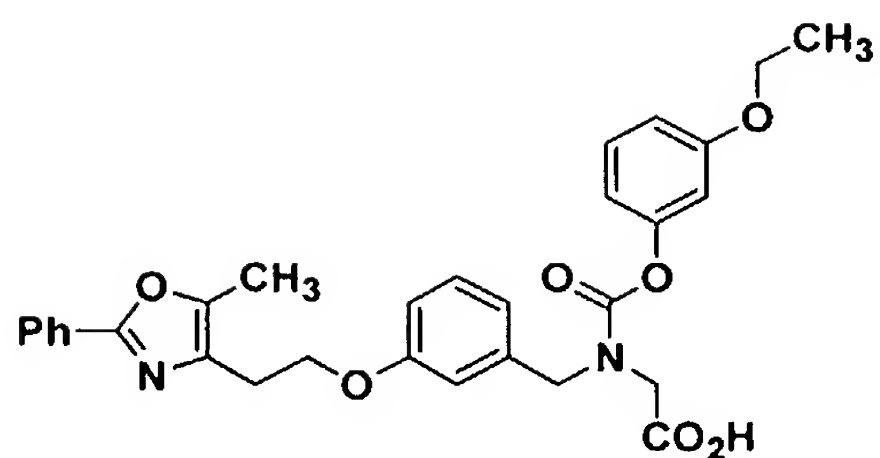
--17. (Amended) The method as defined in Claim 34 wherein the compound employed has the structure



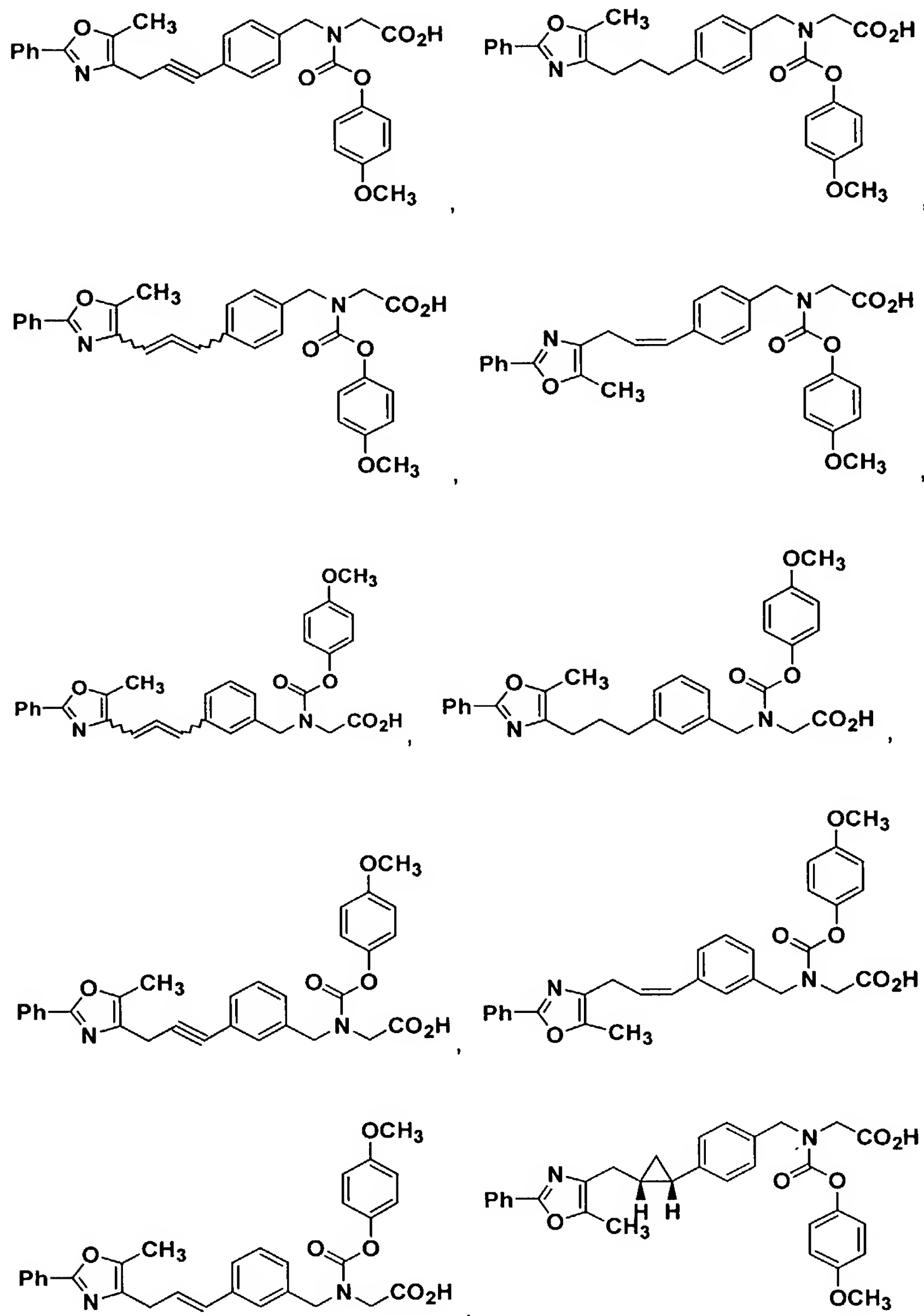


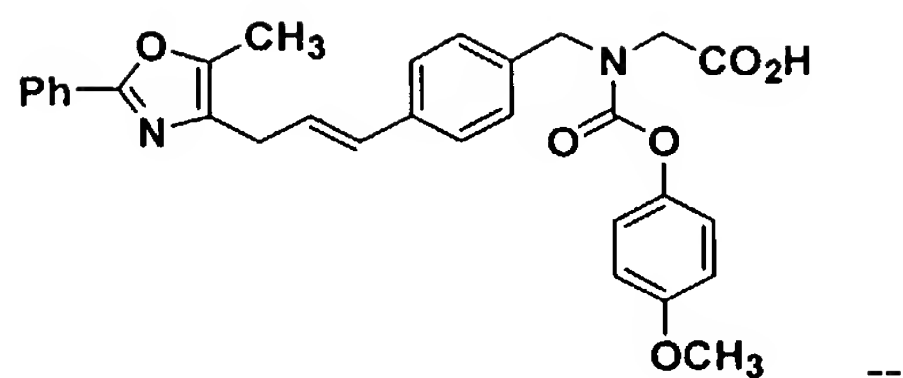
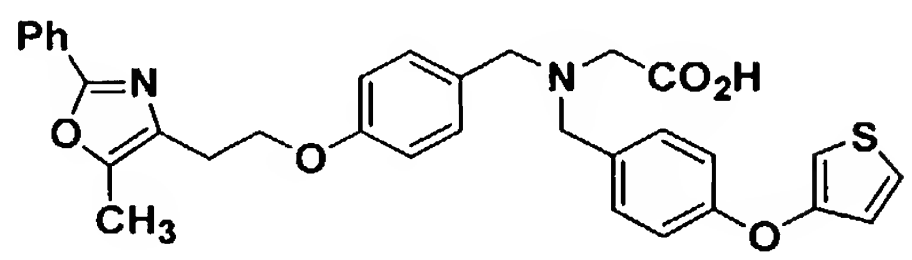
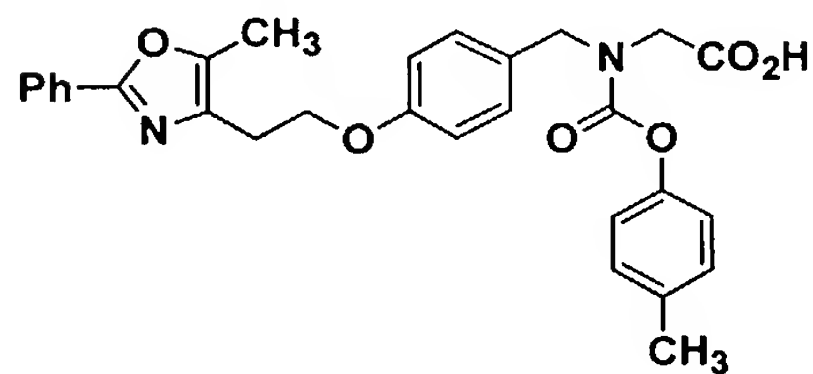
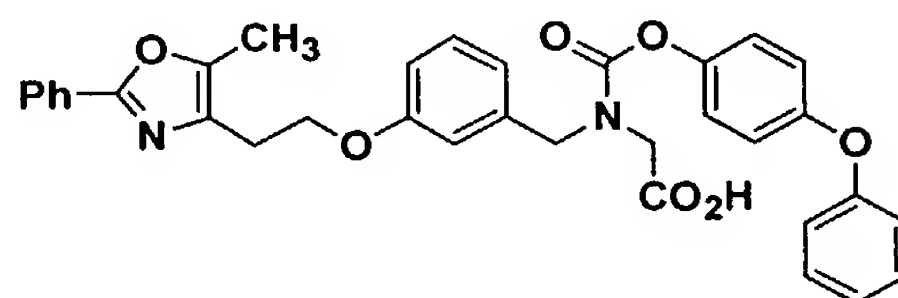
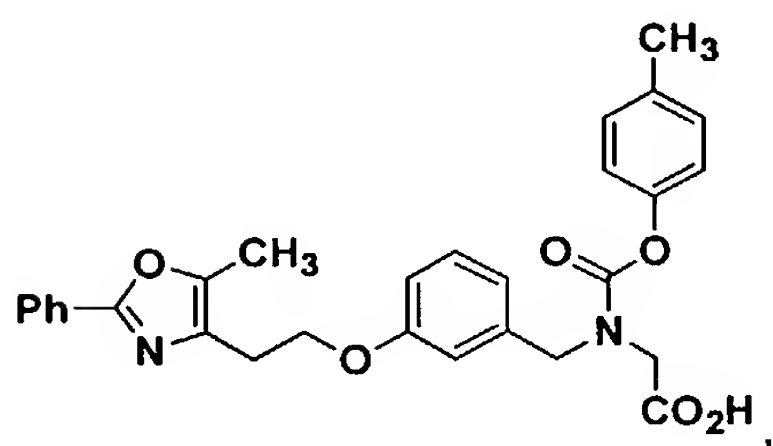
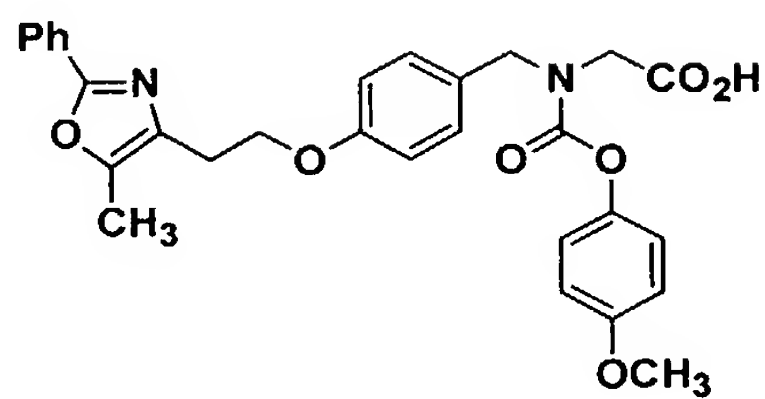
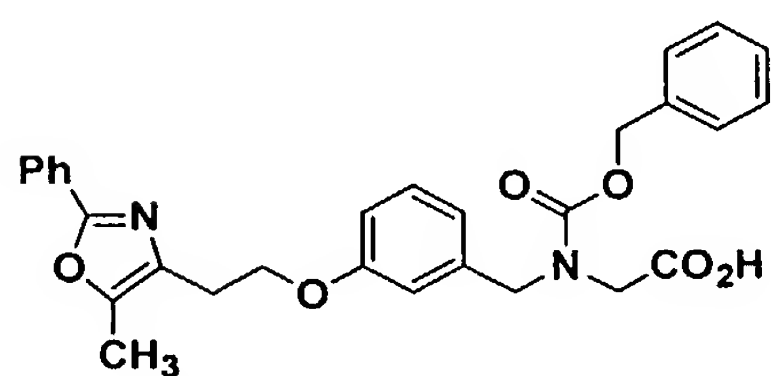




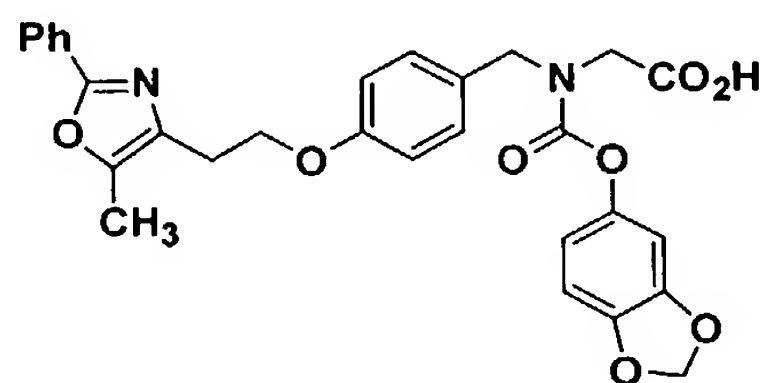
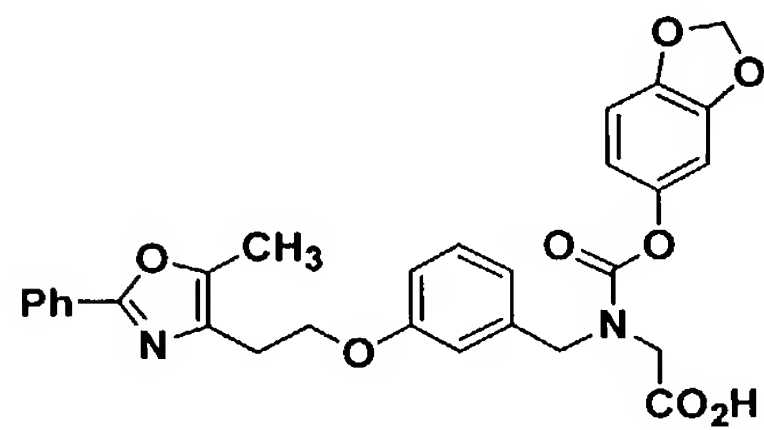
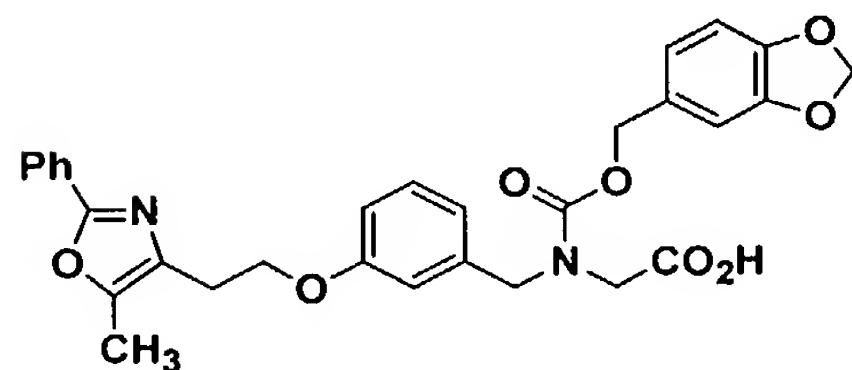
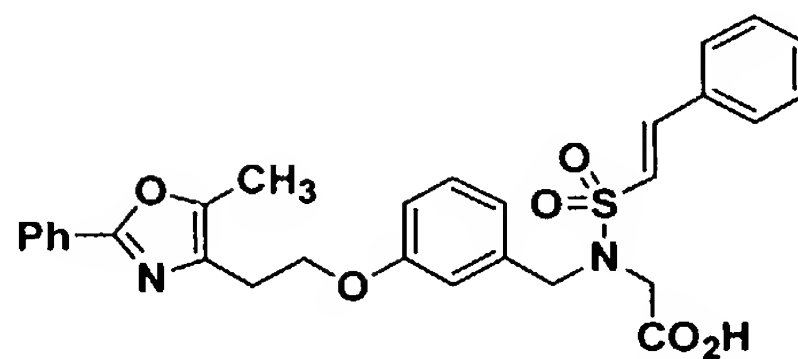
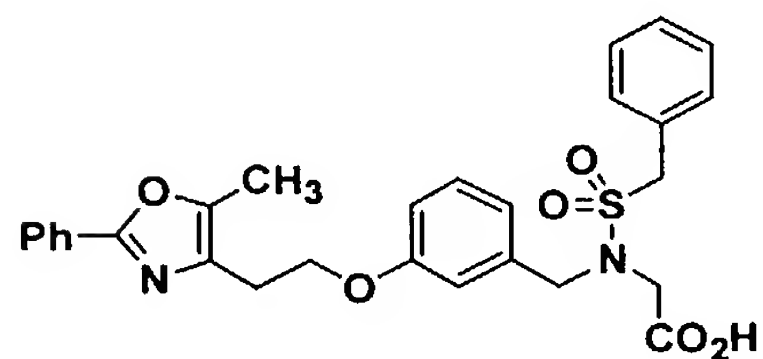
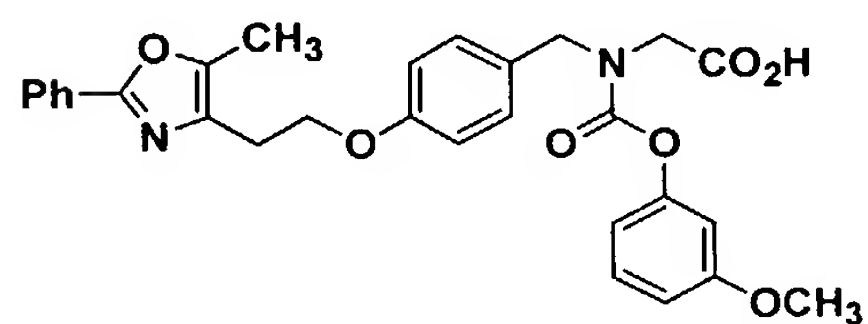
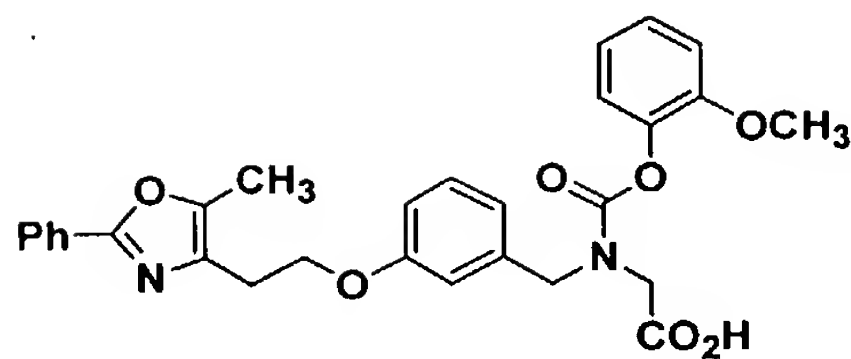
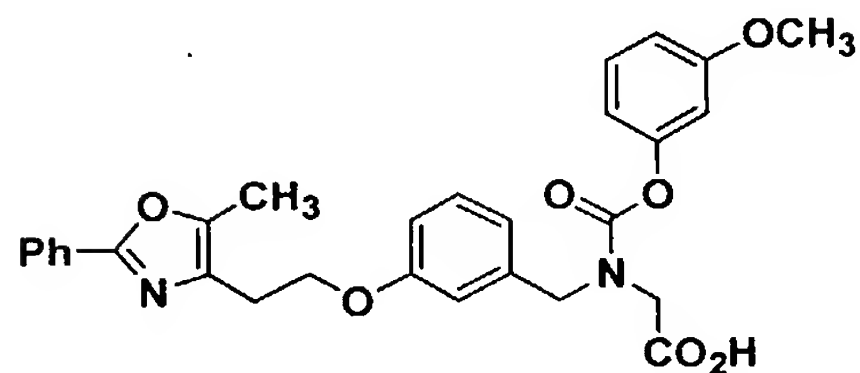
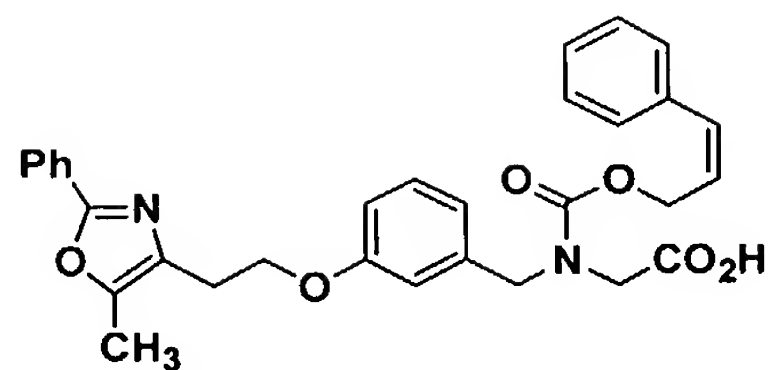


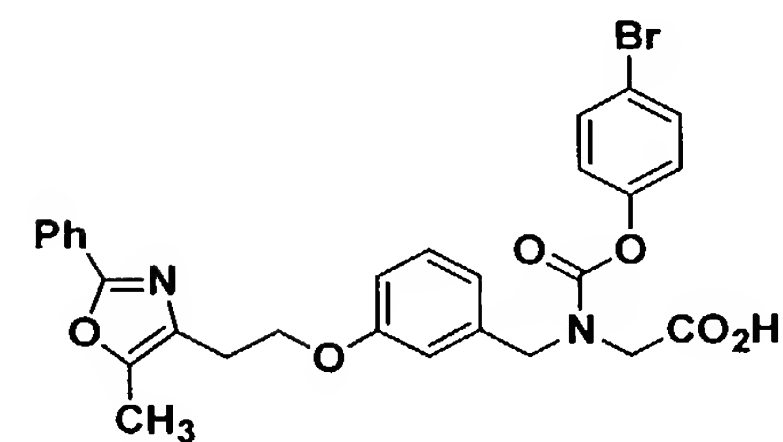
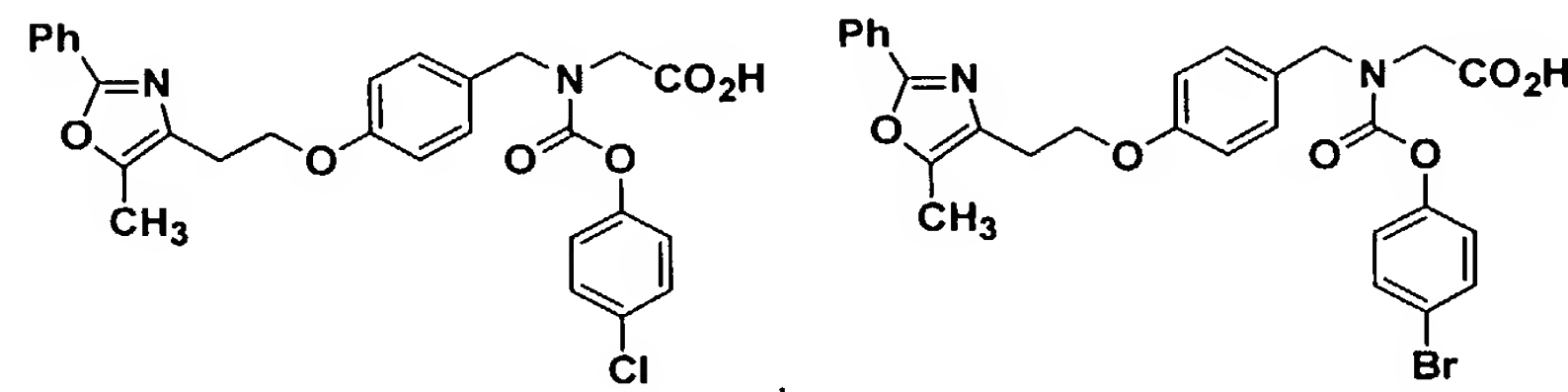
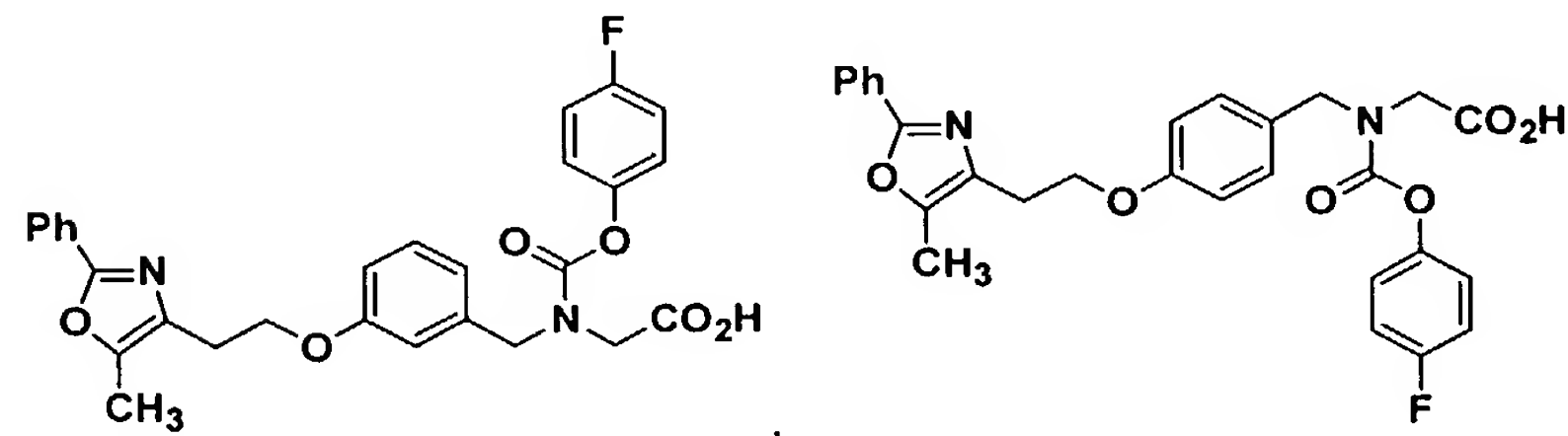
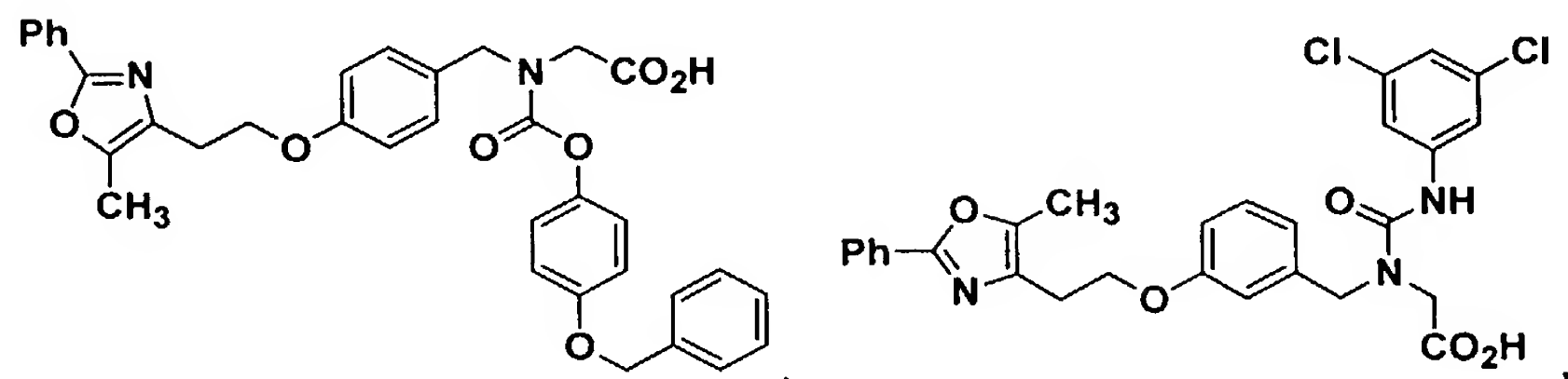
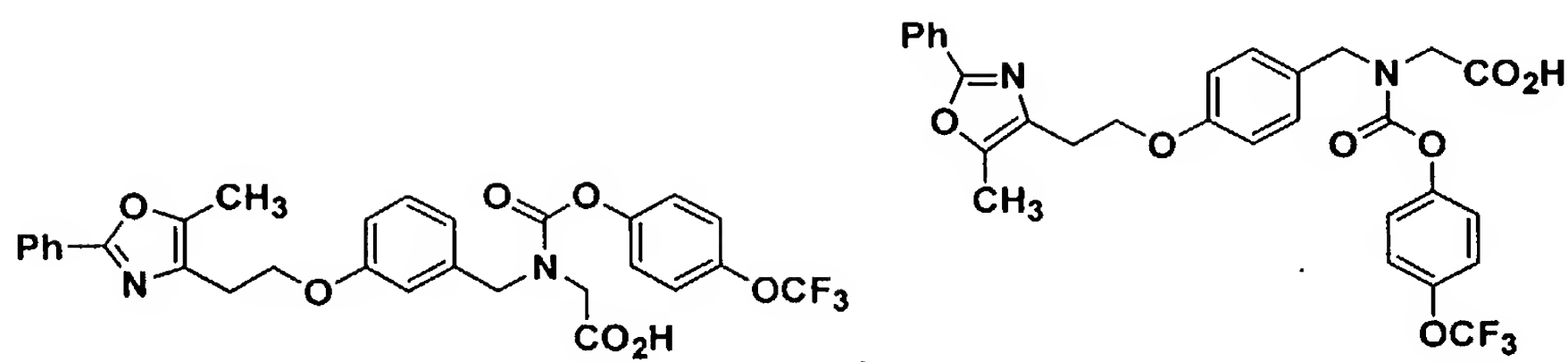
--18. (Amended) The method as defined in Claim 34 wherein the compound employed has the structure

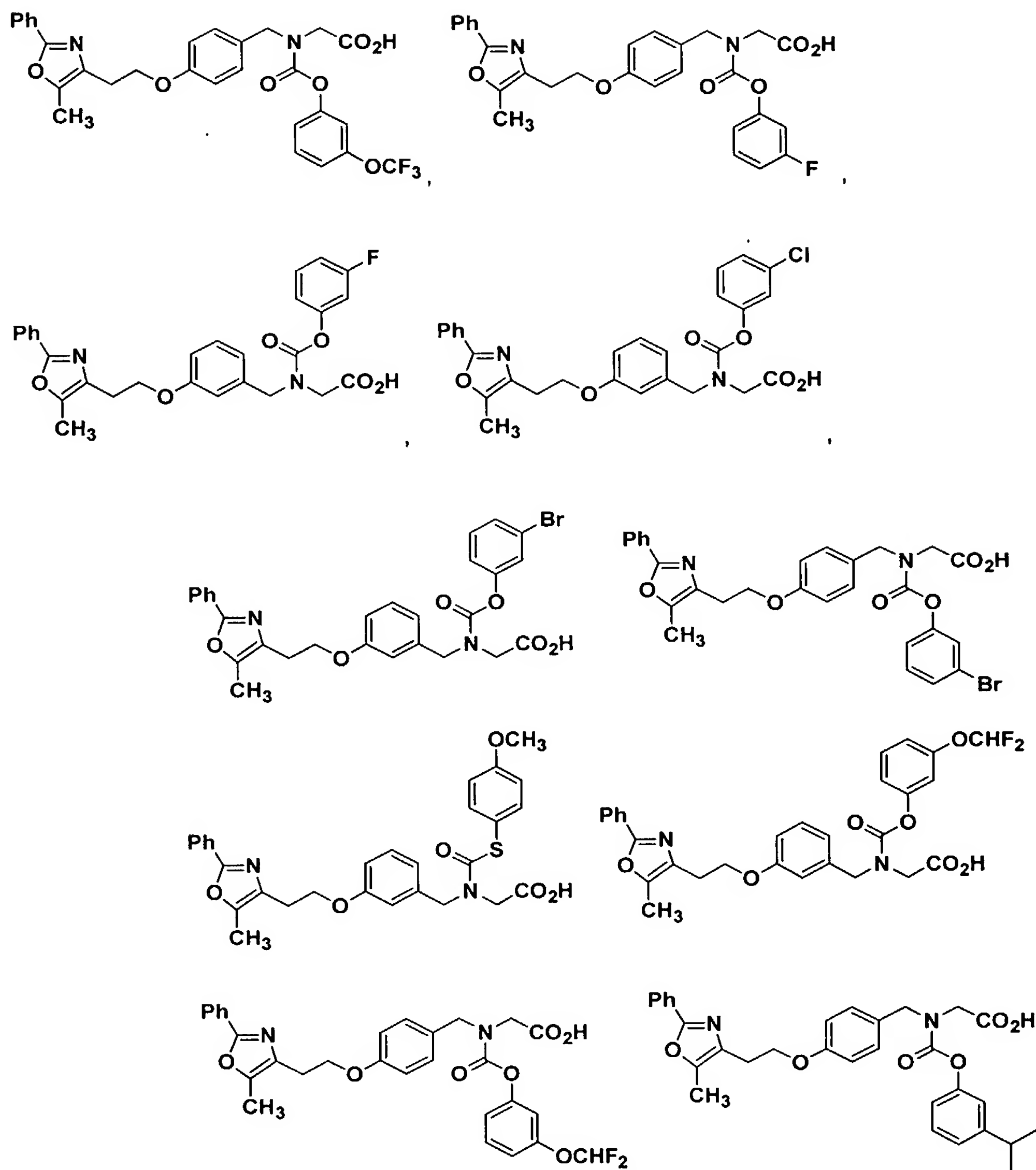


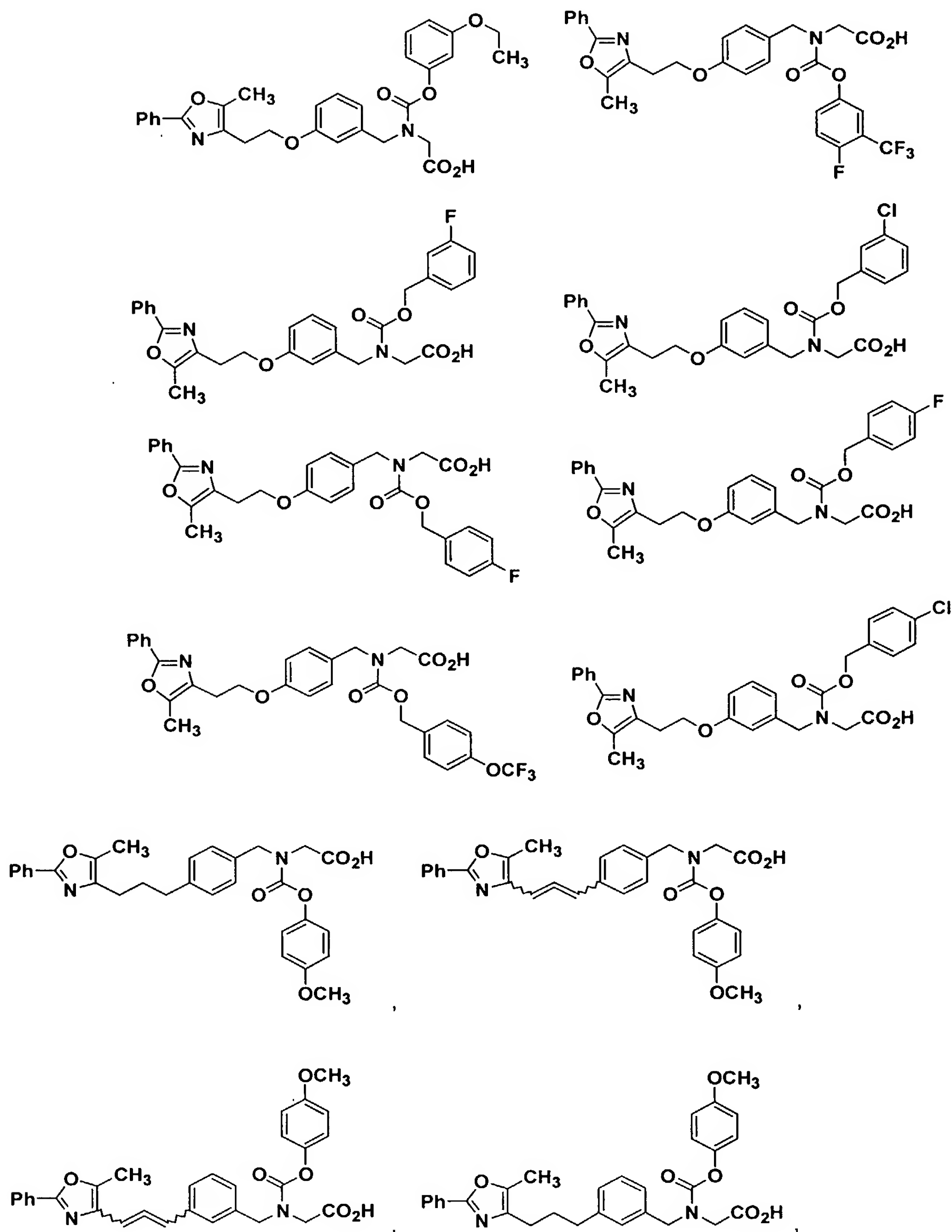
CC1=C(C(=O)OCCN(C1)c2ccccc2)C(=O)OCCN(C1)c2ccccc2

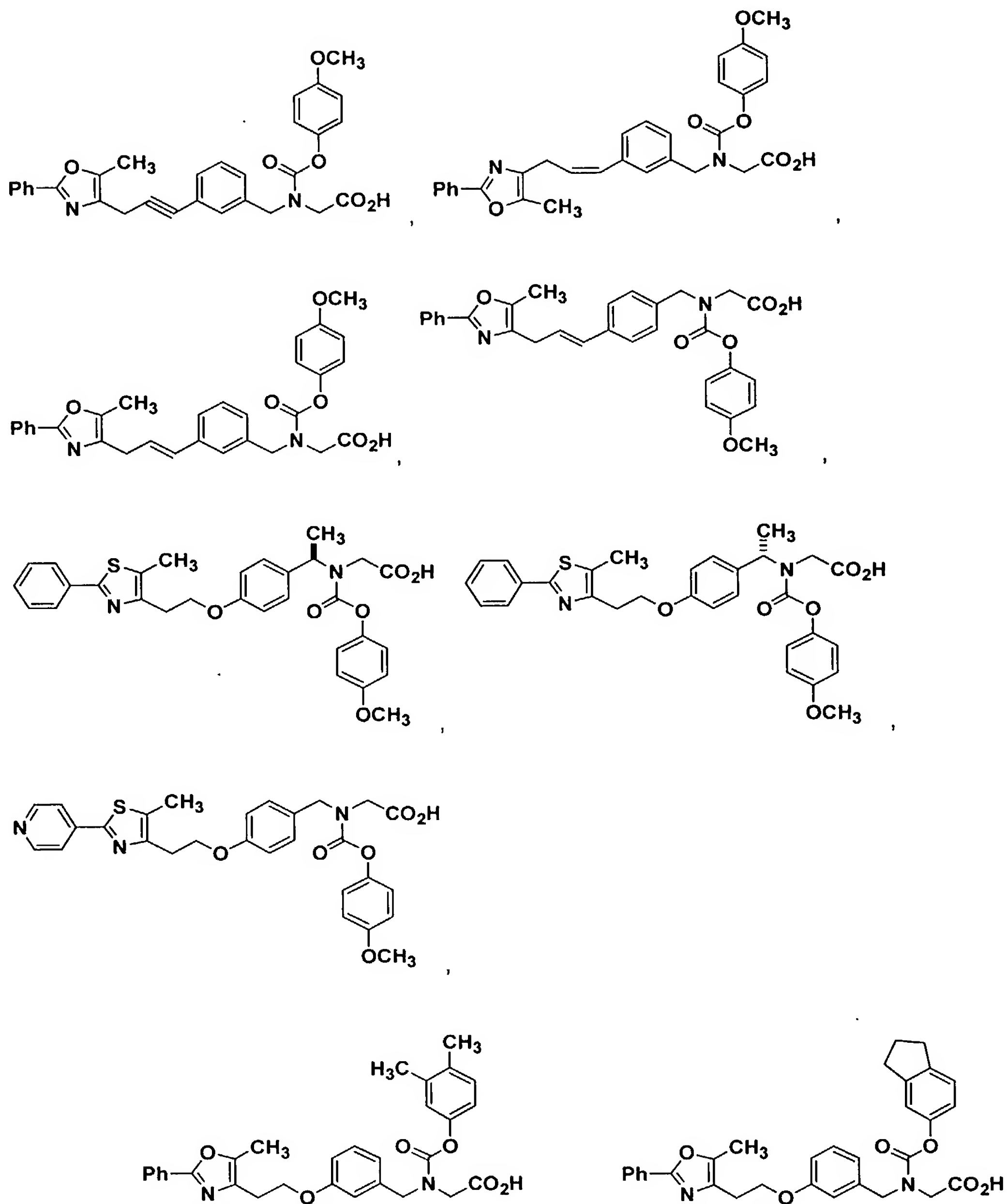


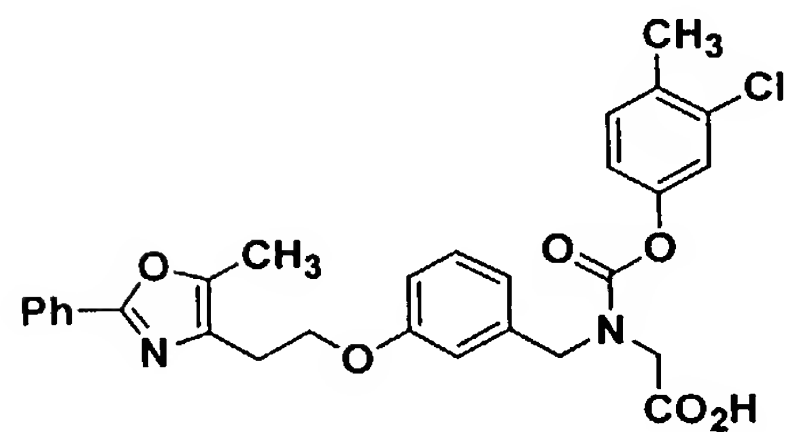
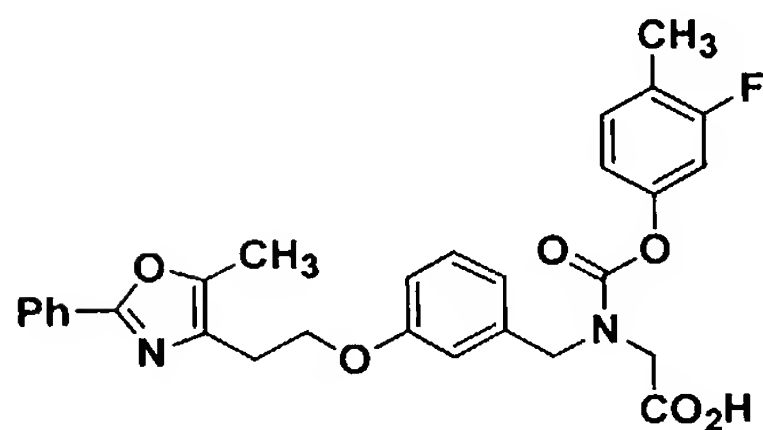
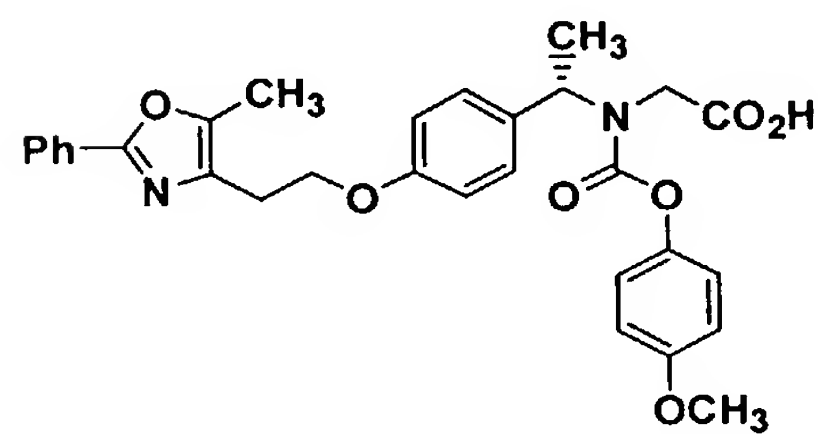
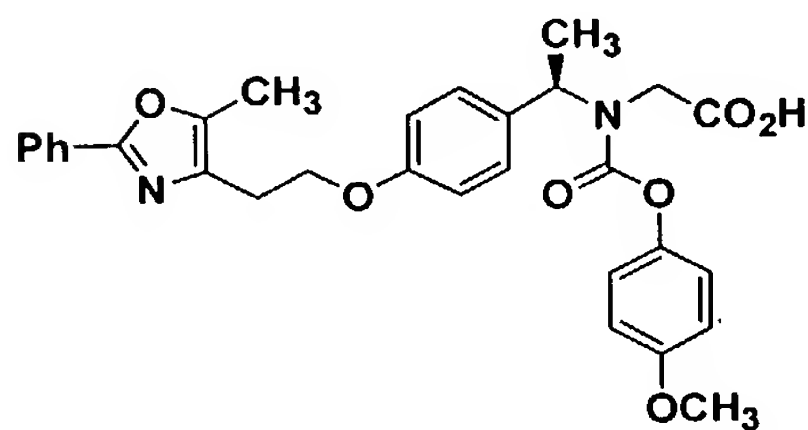
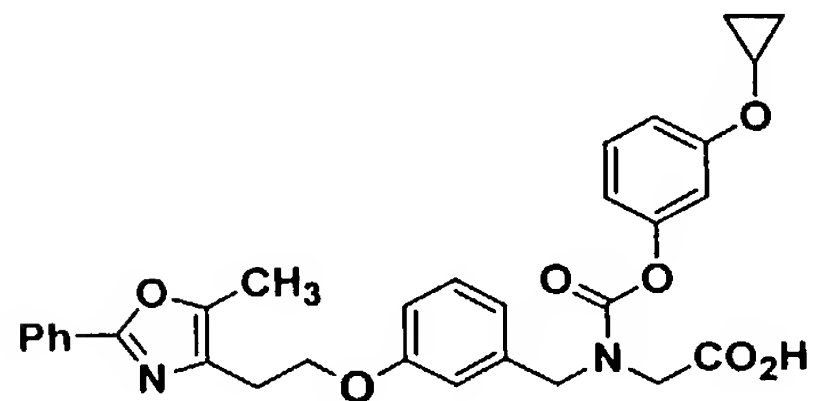
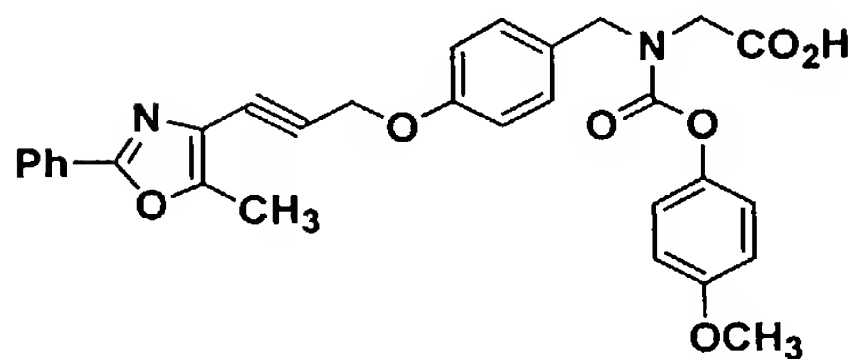
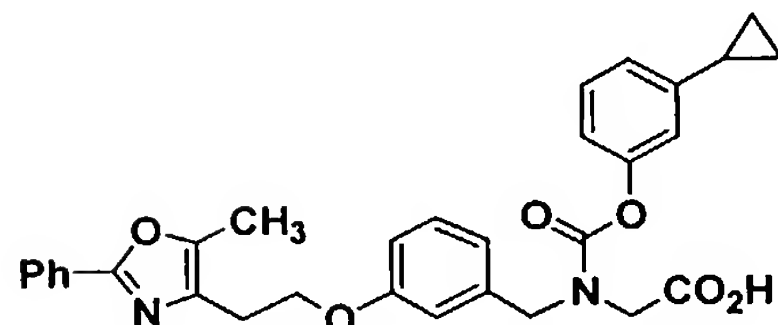
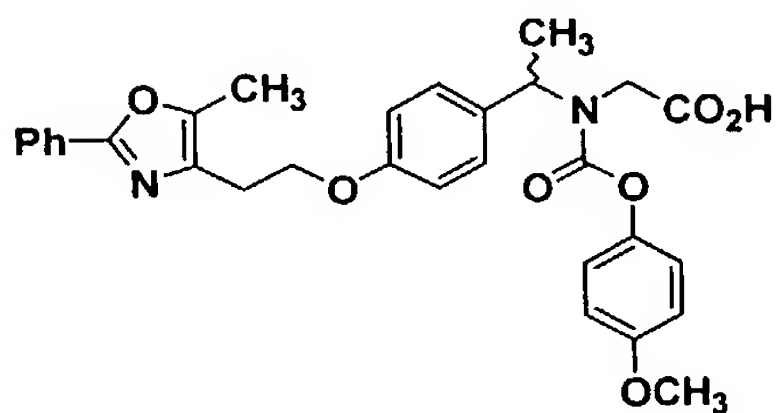
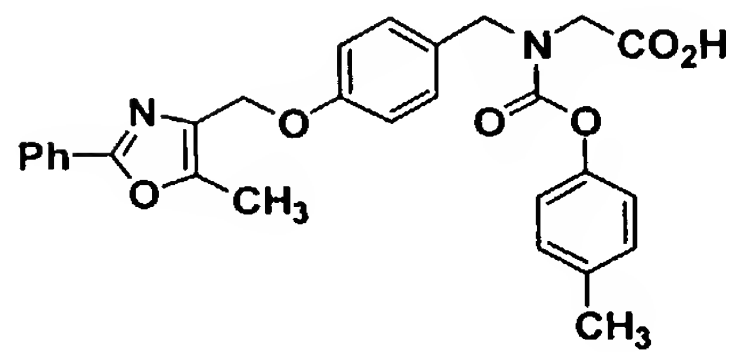
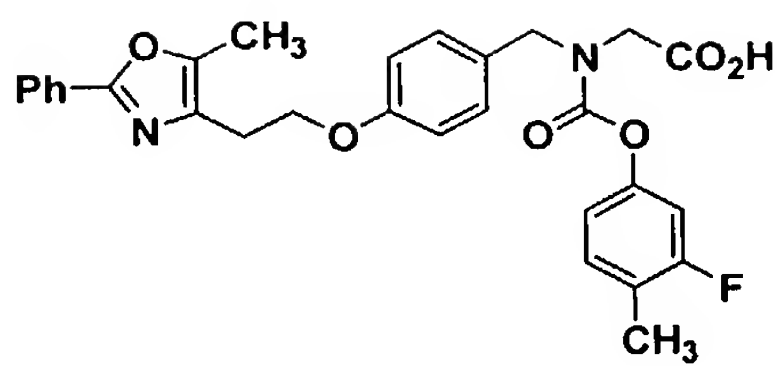


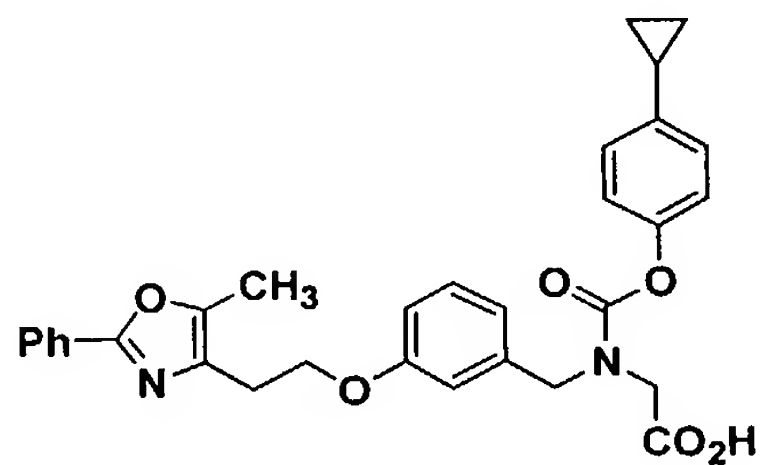
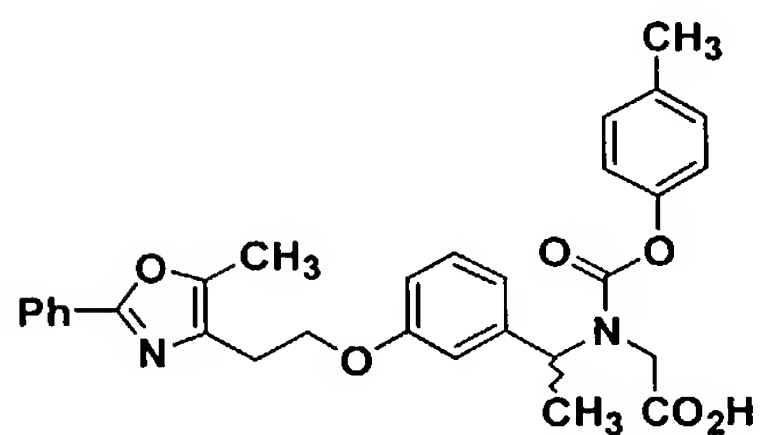
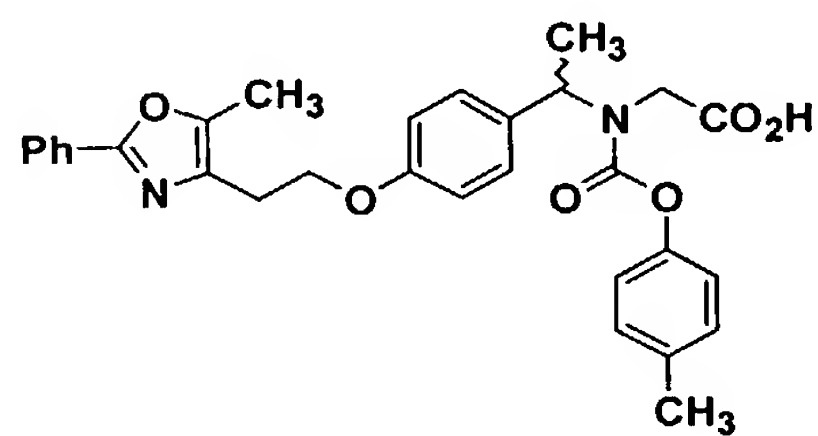
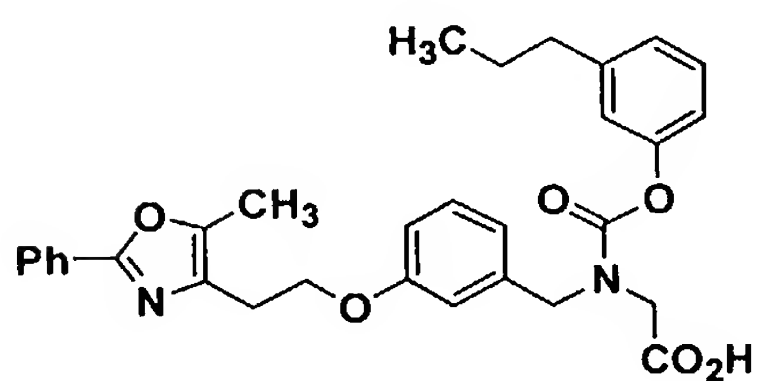
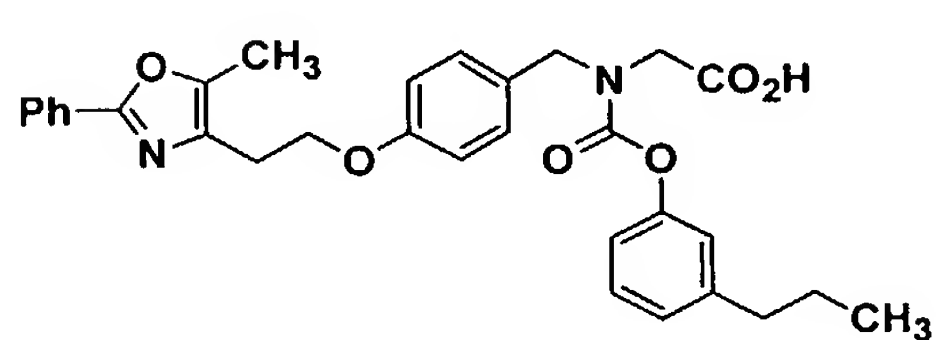
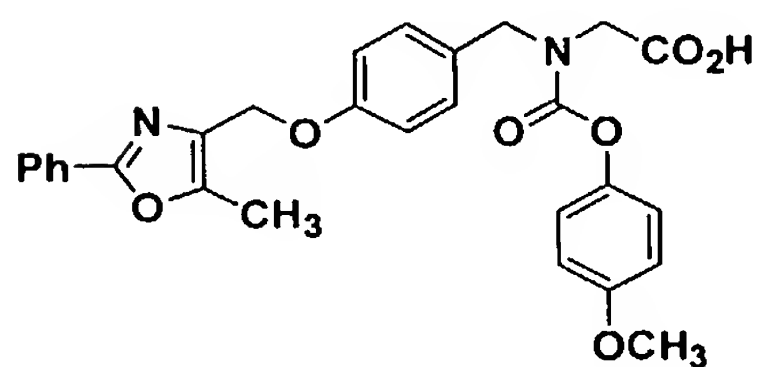
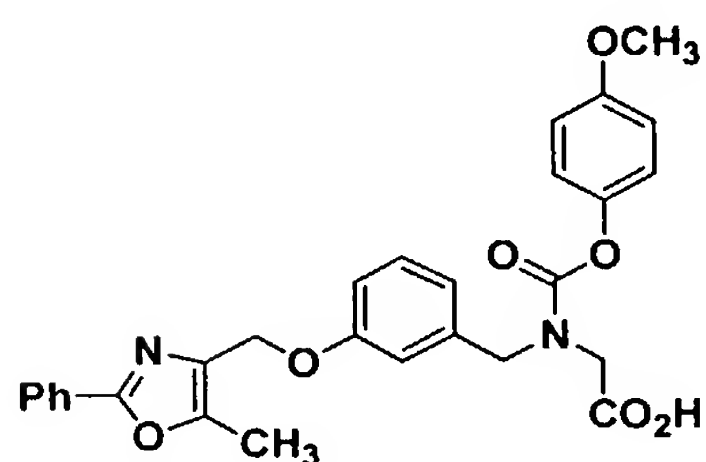
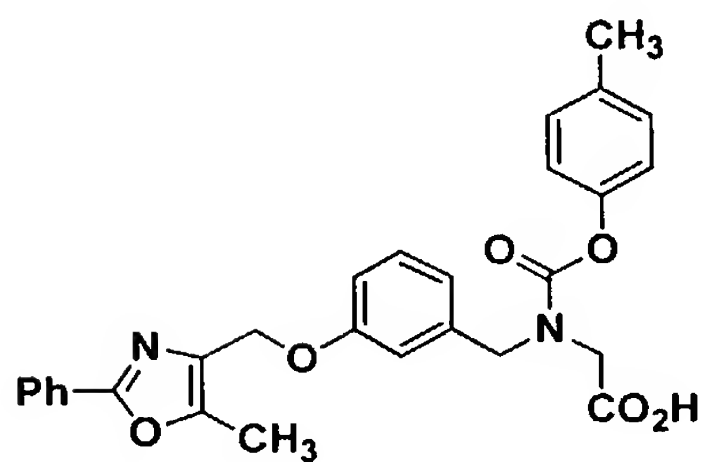
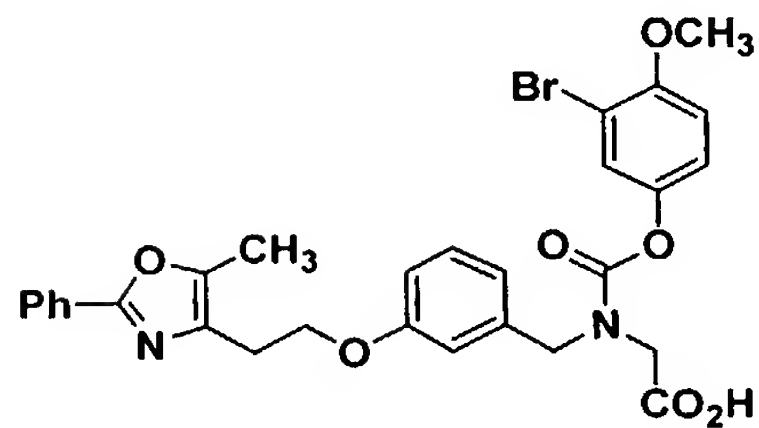
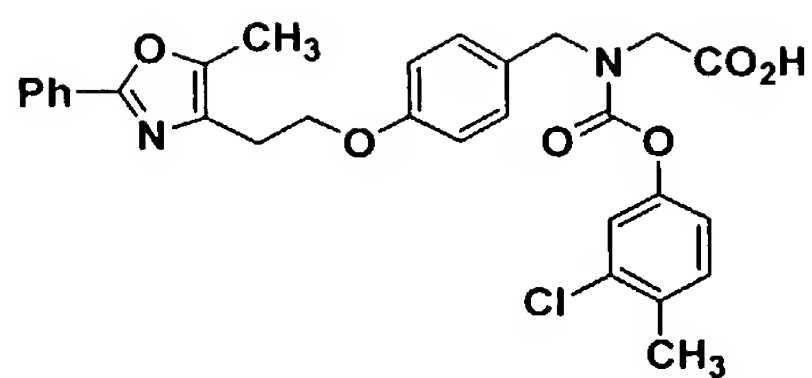


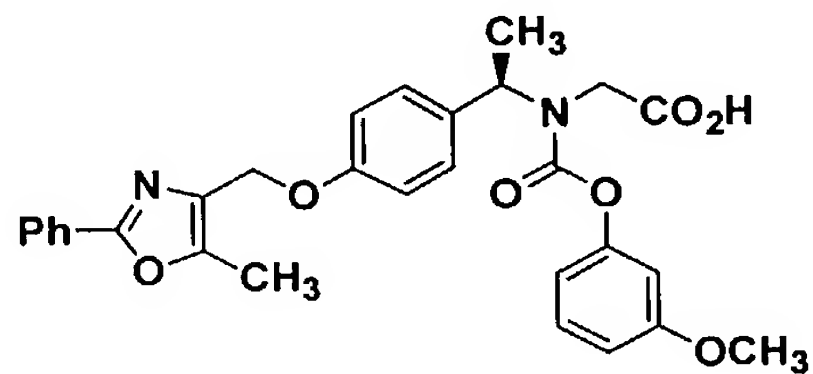
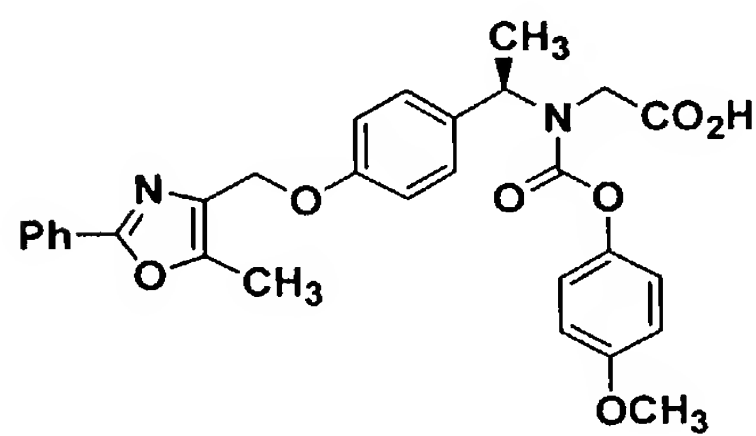
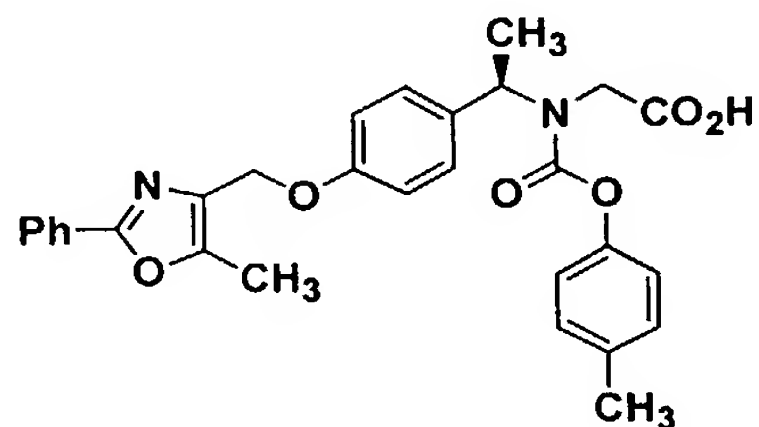
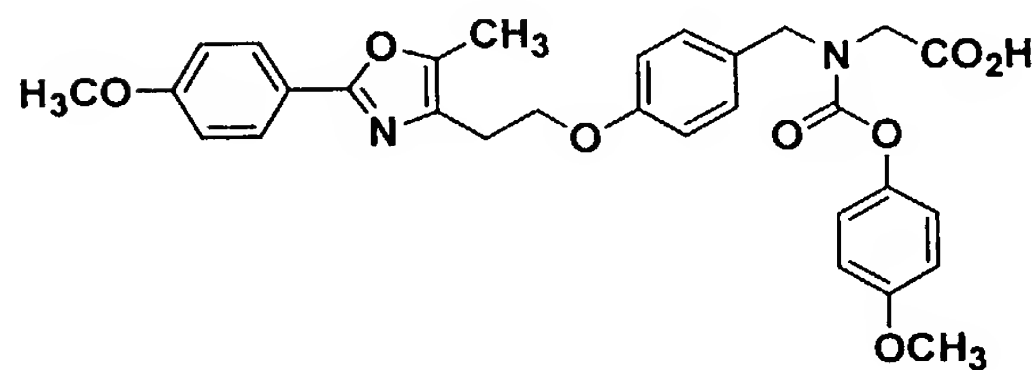
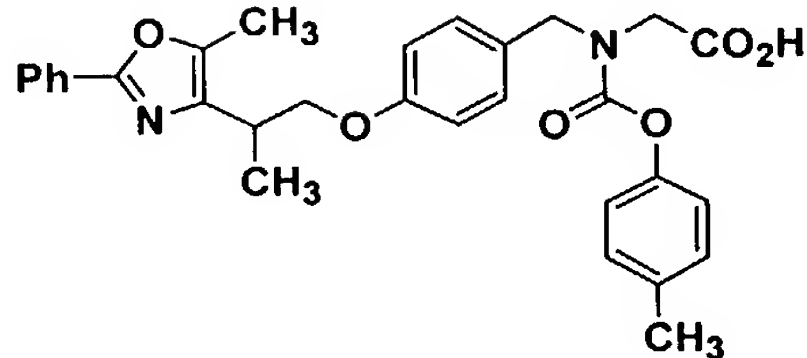
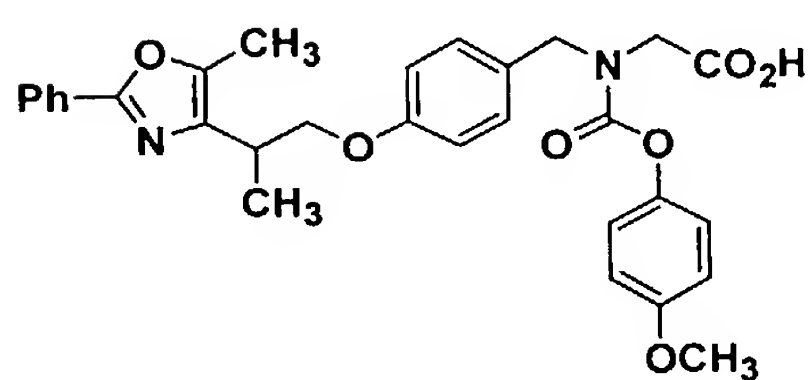
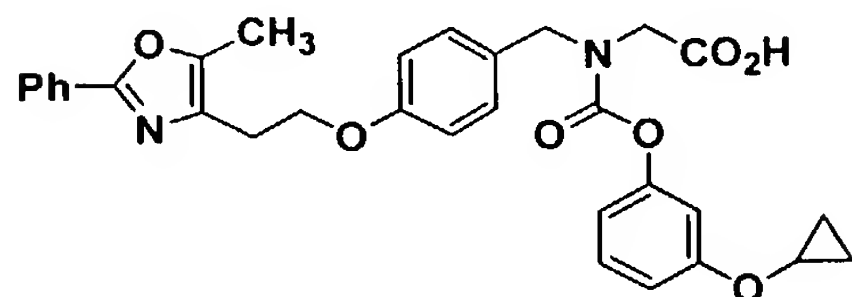
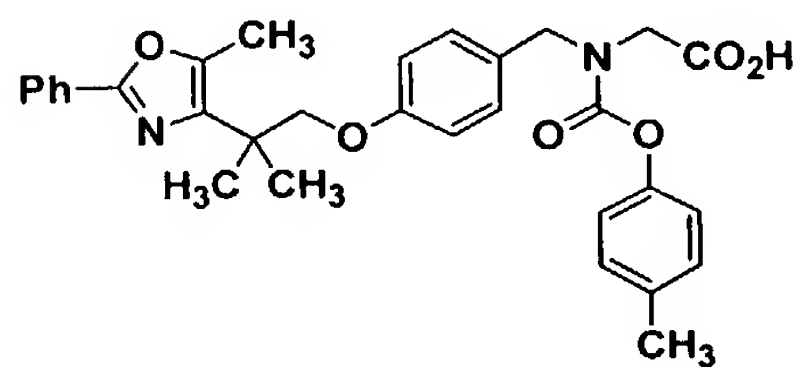
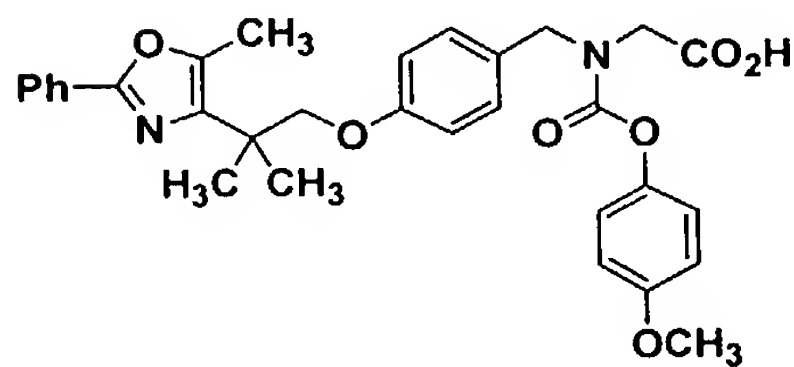
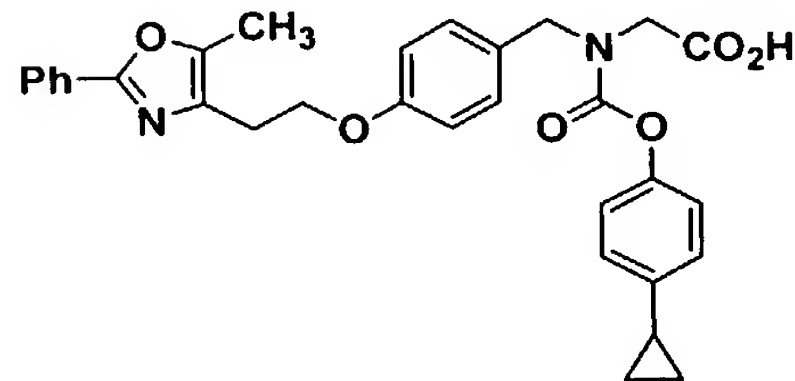
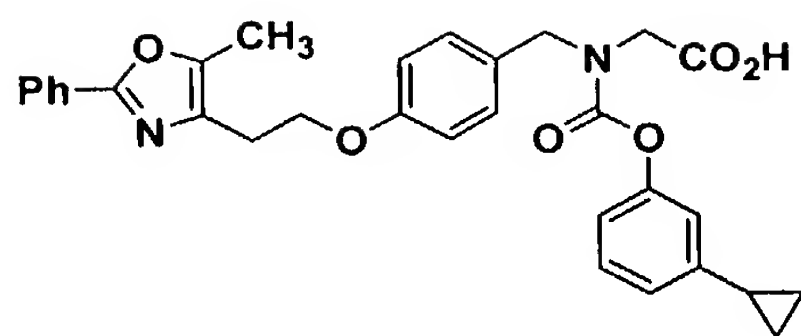




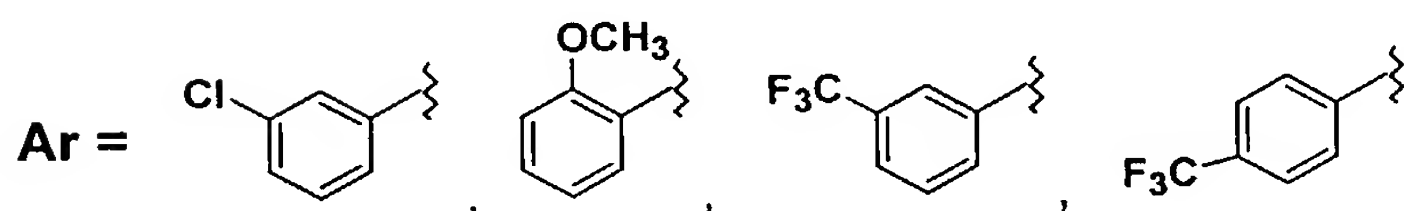
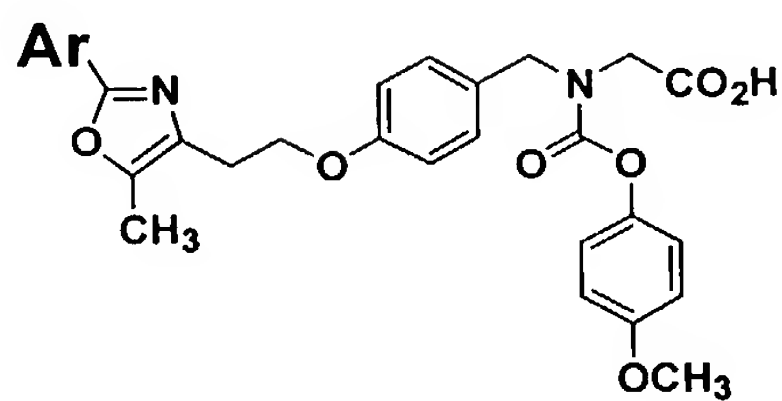
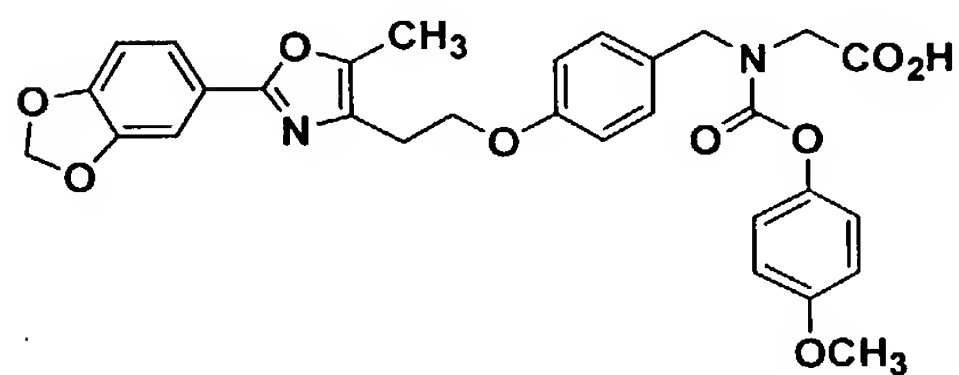
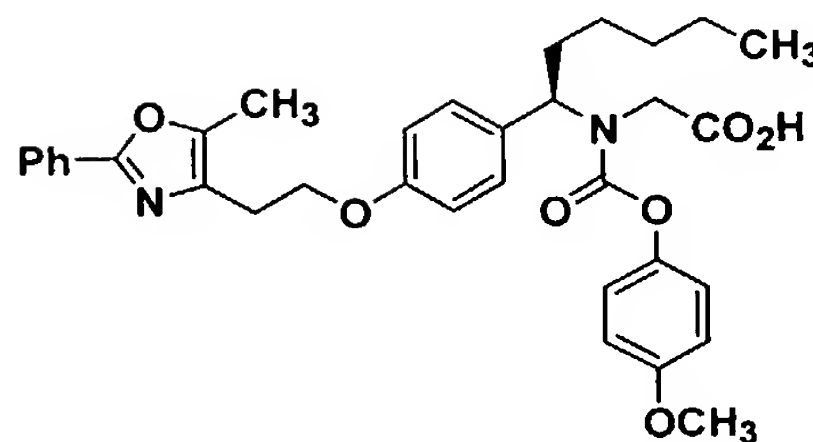
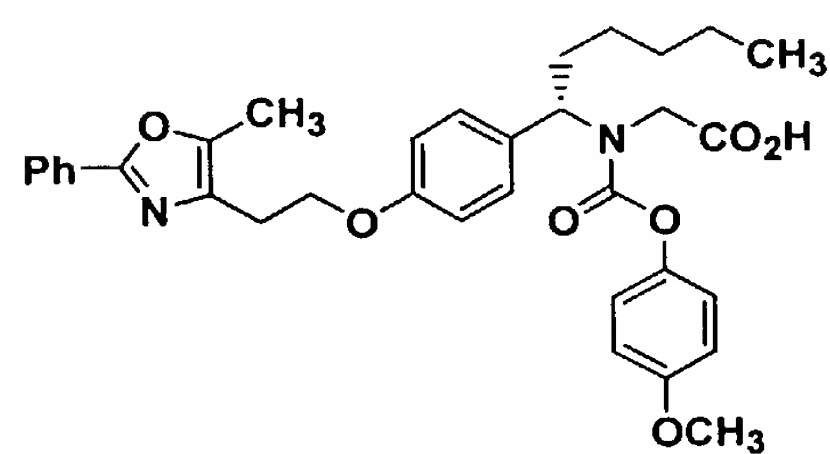
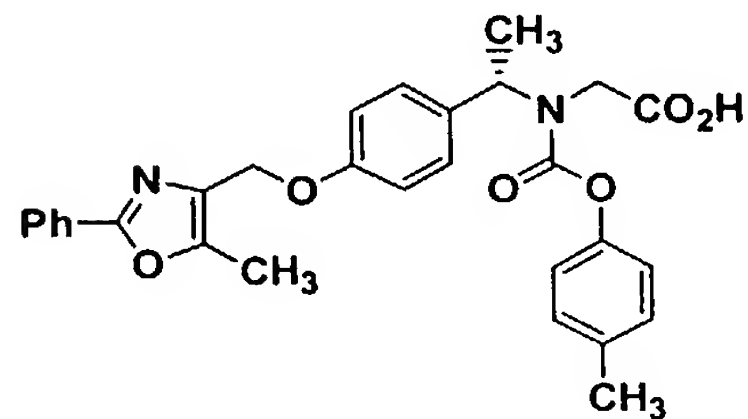
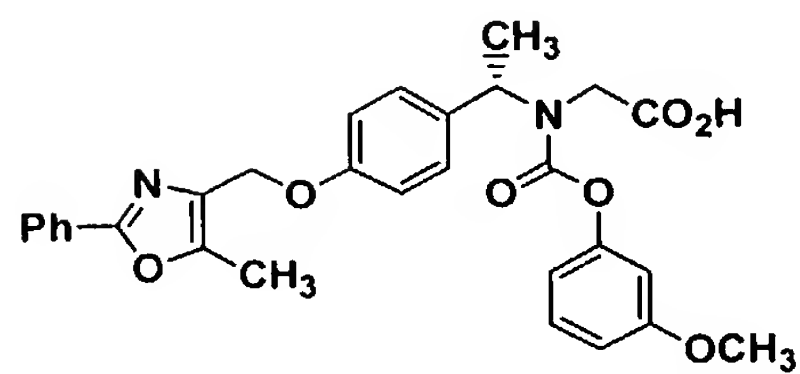
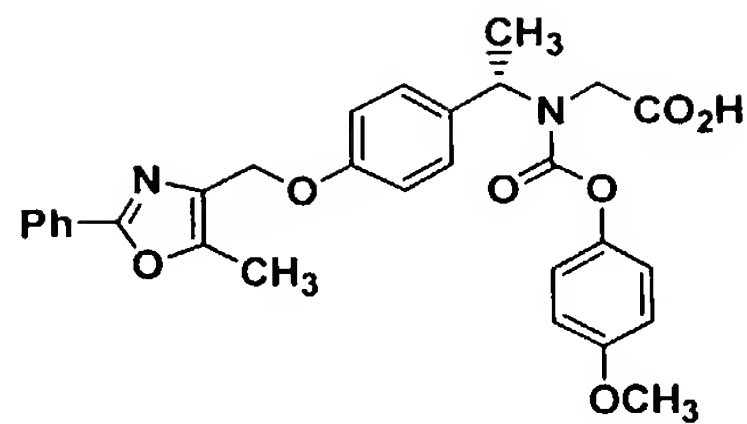


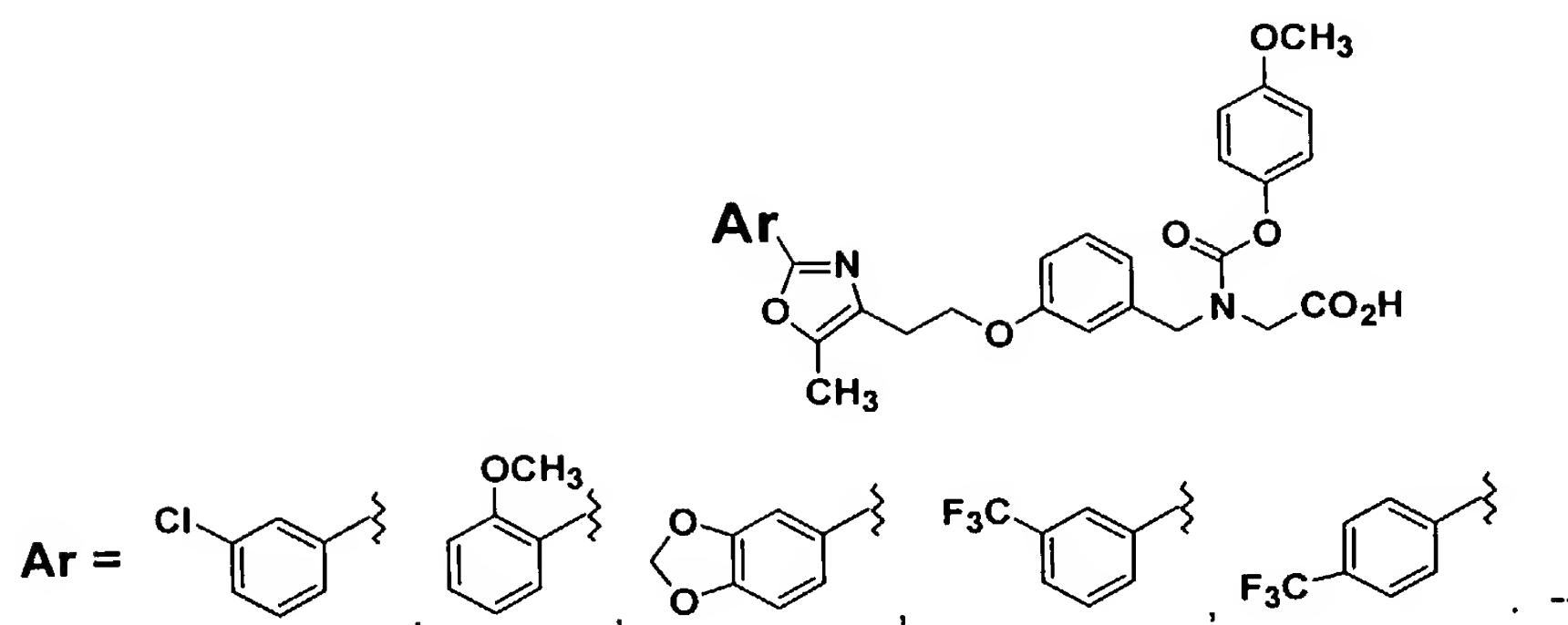




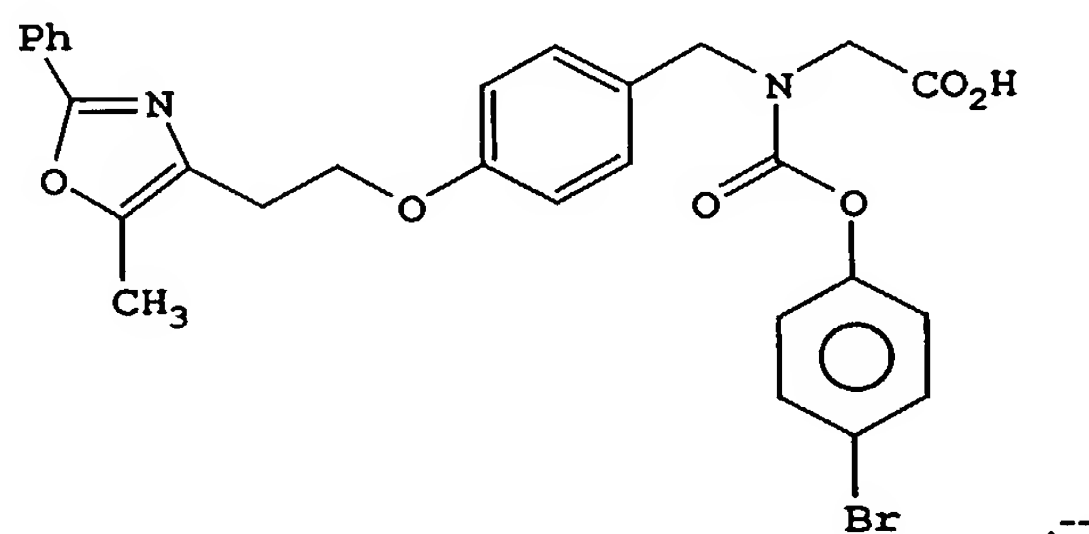




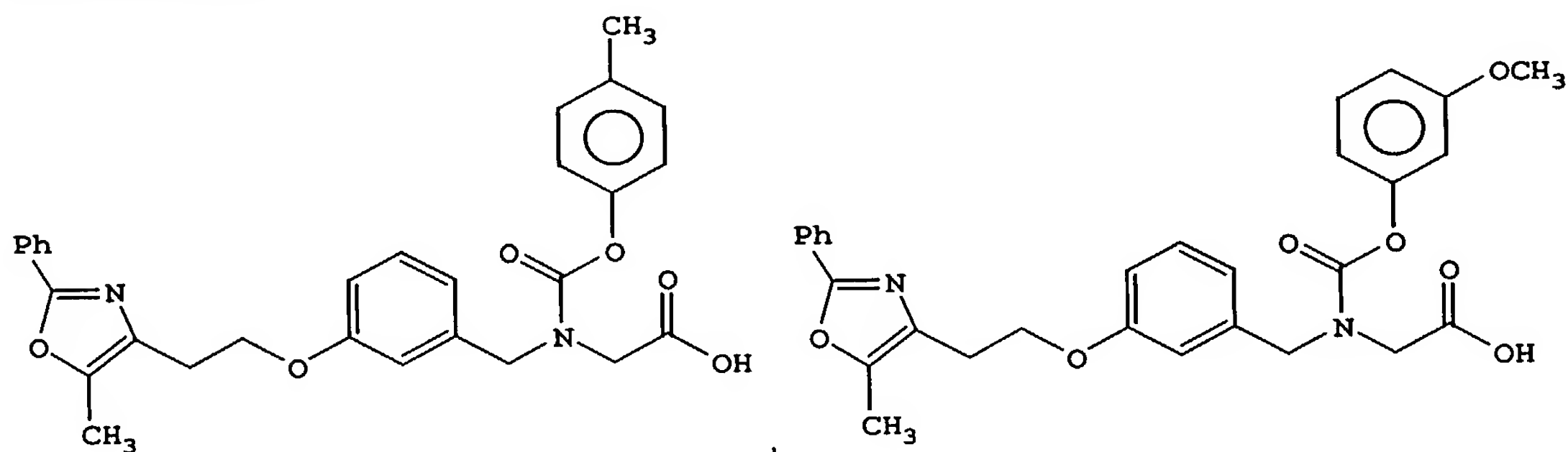


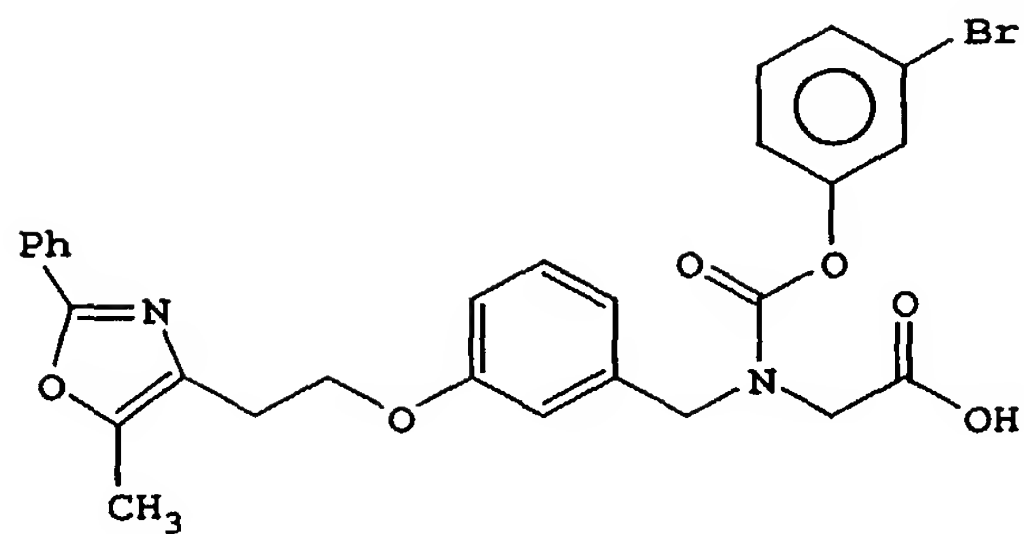


--21. (Amended) The method as defined in Claim 55 wherein the compound employed has the structure

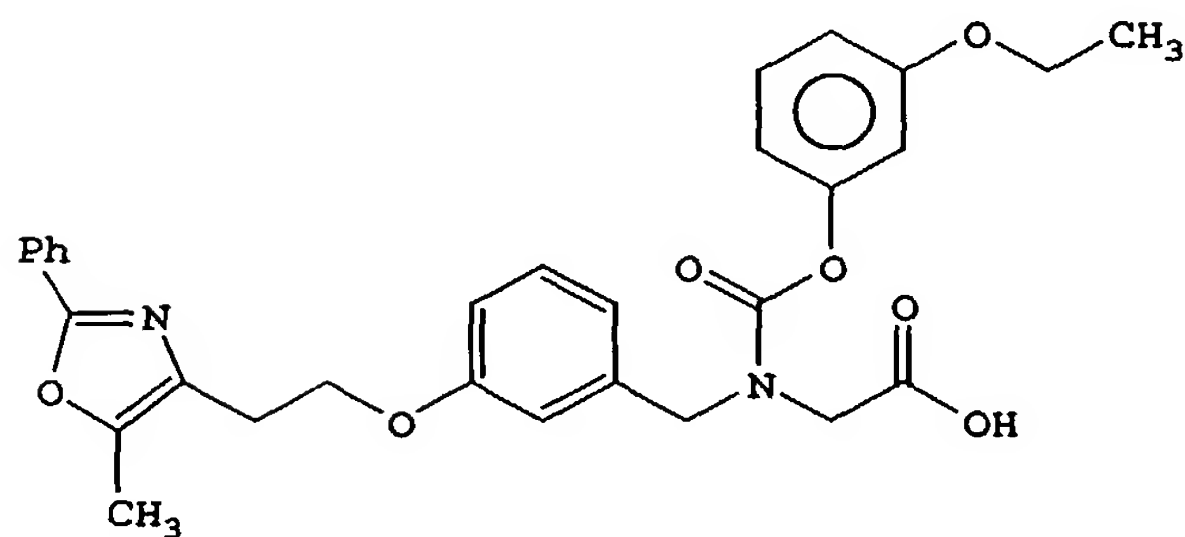


--22. (Amended) The method as defined in Claim 55 wherein the compound employed has the structure

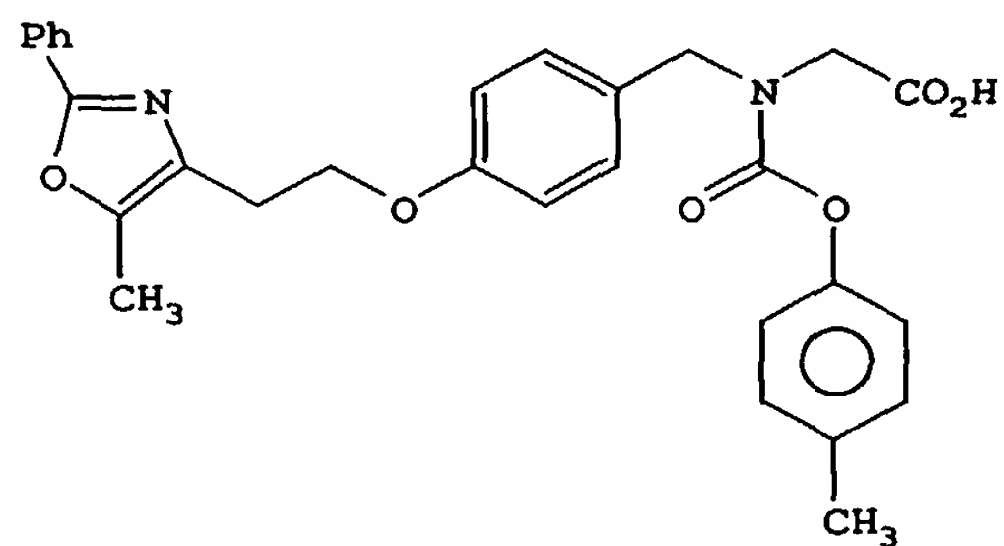




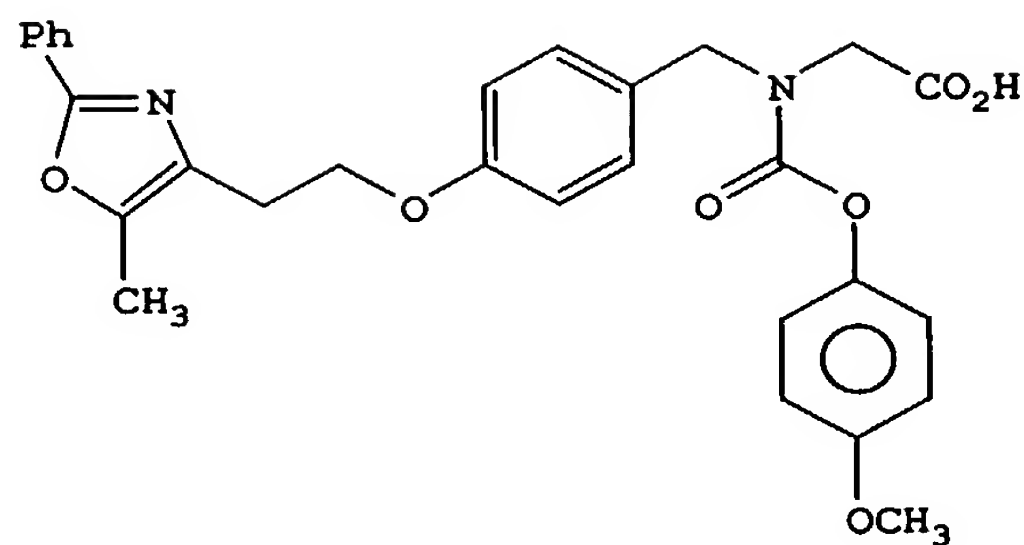
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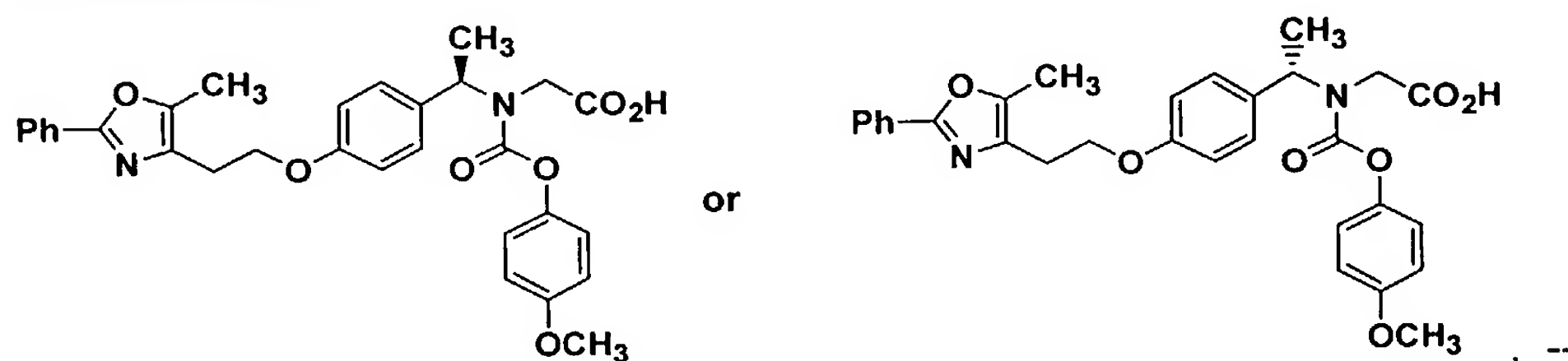
--26. (Amended) The method as defined in Claim 55 wherein the compound employed has the structure



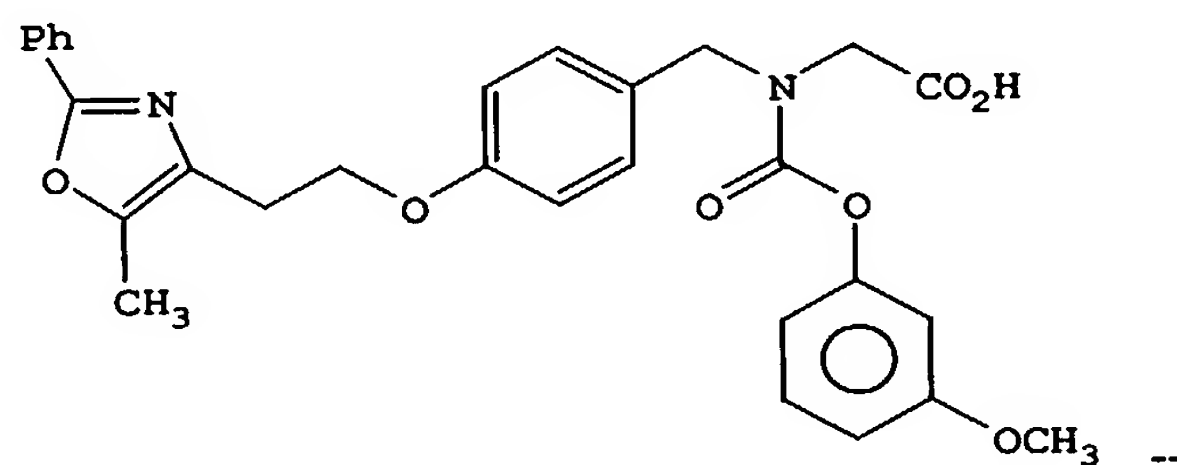
--27. (Amended) The method as defined in Claim 55 wherein the compound employed has the structure



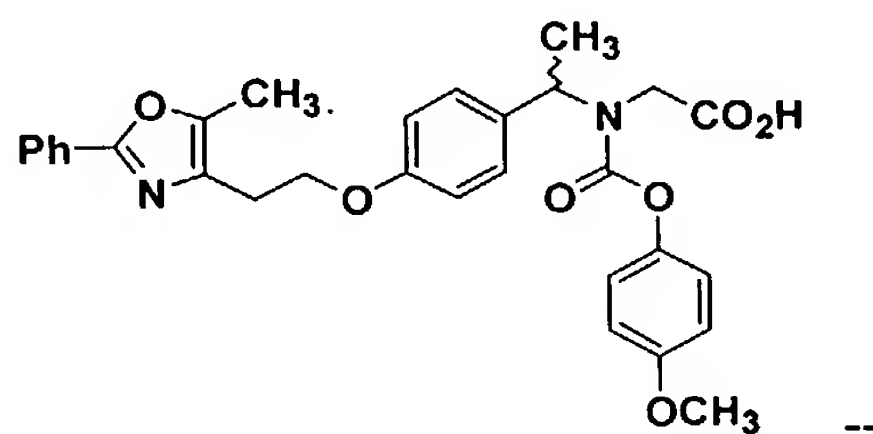
--28. (Amended) The method as defined in Claim 55 wherein the compound employed has the structure



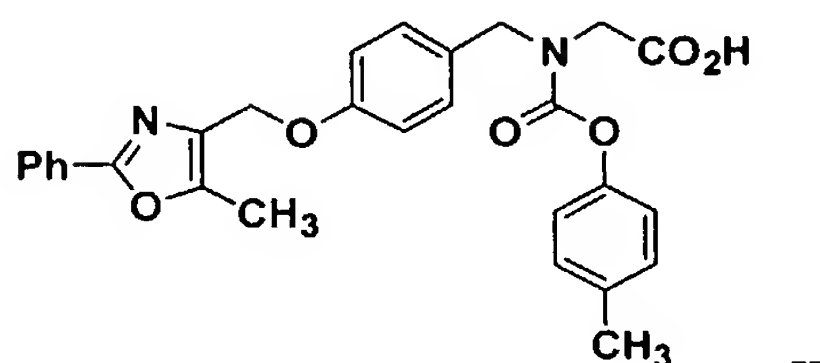
--30. (Amended) The method as defined in Claim 55 wherein the compound employed has the structure



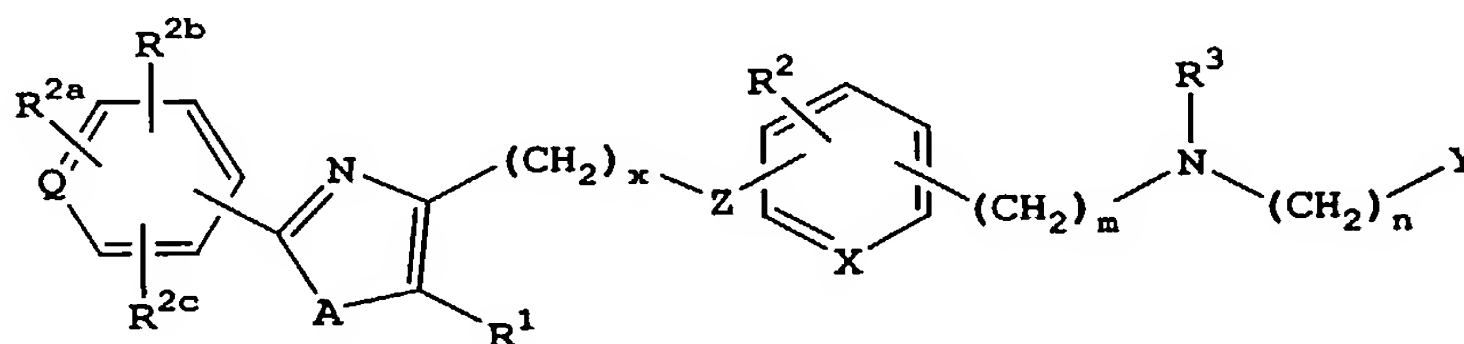
--31. (Amended) The method as defined in Claim 55 wherein the compound employed has the structure



--32. (Amended) The method as defined in Claim 55 wherein the compound employed has the structure



--34. (Amended) A method for lowering blood glucose levels or for treating diabetes, or for treating a premalignant disease, an early malignant disease, a malignant disease, or a dysplastic disease, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound which has the structure



wherein x is 1,2, 3 or 4; m is 1 or 2; n is 1 or 2;

Q is C or N;

A is O or S;

Z is O or a bond;

R<sup>1</sup> is H or lower alkyl;

X is CH;

R<sup>2</sup> is H, alkyl, alkoxy, halogen, amino or substituted amino;

R<sup>2a</sup>, R<sup>2b</sup> and R<sup>2c</sup> are the same or different and are selected from H, alkyl, alkoxy, halogen, amino or substituted amino;

R<sup>3</sup> is aryloxycarbonyl, alkyloxycarbonyl, alkynyloxycarbonyl, alkenyloxycarbonyl, alkyl(halo)aryloxycarbonyl, alkyloxy(halo)aryloxycarbonyl, cycloalkylaryloxycarbonyl, cycloalkyloxyaryloxycarbonyl, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, alkoxycarbonylamino, aryloxycarbonylamino, heteroaryloxycarbonylamino, alkylsulfonyl, alkenylsulfonyl, heteroaryloxycarbonyl, cycloheteroalkyloxycarbonyl, heteroarylalkenyl, hydroxyalkyl, alkoxy, alkoxyaryloxycarbonyl, arylalkyloxycarbonyl, alkylaryloxycarbonyl,

or stereoisomers thereof, prodrug esters thereof, and pharmaceutically acceptable salts thereof. --

- 48 -

alkynyloxycarbonyl, haloalkoxyaryloxycarbonyl, alkoxycarbonylaryloxycarbonyl, aryloxyaryloxycarbonyl, arylalkenyloxycarbonyl, heteroaryloxyarylalkyl, aryloxyarylalkyloxycarbonyl, aryloxyalkyloxycarbonyl, arylalkylsulfonyl, arylthiocarbonyl, arylalkenylsulfonyl, heteroarylsulfonyl, arylsulfonyl, heteroarylalkoxycarbonyl, heteroarylalkyloxyarylalkyl, arylalkenylarylalkyl, arylalkoxycarbonylheteroarylalkyl, heteroaryloxyarylalkyl, arylalkenylheteroarylalkyl or polyhaloalkylaryloxycarbonyl;

Y is  $\text{CO}_2\text{R}^4$  where  $\text{R}^4$  is H or alkyl, or a prodrug ester or Y is a C-linked 1-tetrazole, a phosphinic acid of the structure  $\text{P}(\text{O})(\text{OR}^{4a})\text{R}^5$  where  $\text{R}^{4a}$  is H or a prodrug ester,  $\text{R}^5$  is alkyl or aryl or a phosphonic acid of the structure  $\text{P}(\text{O})(\text{OR}^{4a})_2$  where  $\text{R}^{4a}$  is H or a prodrug ester;

or stereoisomers thereof, prodrug esters thereof, and pharmaceutically acceptable salts thereof, and a lipid-lowering agent, a lipid modulating agent, an antidiabetic agent, an anti-obesity agent, an antihypertensive agent, a platelet aggregation inhibitor, and/or an antiosteoporosis agent. --

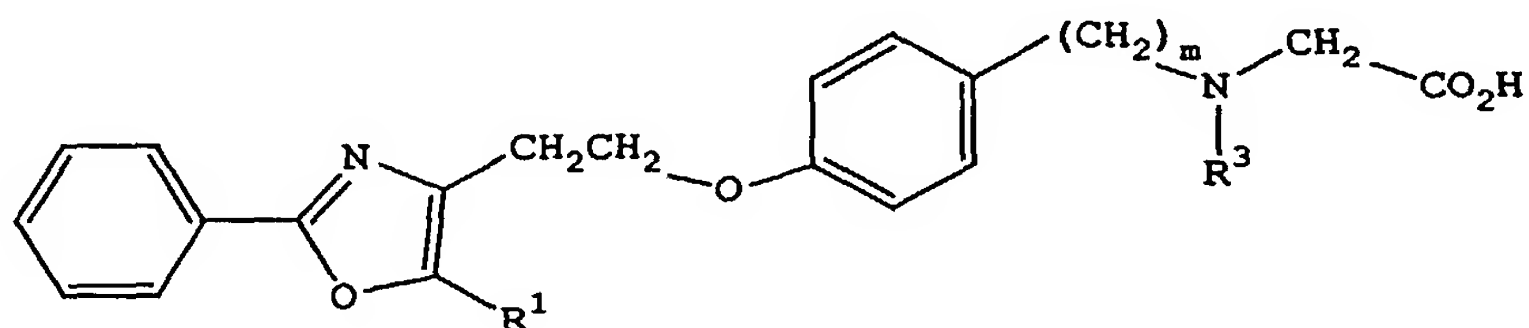
--39. (Amended) The combination as defined in Claim 37 wherein the antidiabetic agent is 1, 2, 3 or more of a biguanide, a sulfonyl urea, a glucosidase inhibitor, a  $\text{PPAR}\alpha$  agonist, a  $\text{PPAR}\gamma$  agonist, a  $\text{PPAR}\alpha/\gamma$  dual agonist, an SGLT2 inhibitor, a DP4 inhibitor, an  $\text{aP2}$  inhibitor, an insulin sensitizer, a glucagon-like peptide-I (GLP-I), insulin and/or a meglitinide; the anti-obesity agent is a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake inhibitor, a thyroid receptor agonist, an  $\text{aP2}$  inhibitor and/or an anorectic agent; the lipid lowering agent is an MTP inhibitor, an HMG CoA reductase inhibitor, a squalene synthetase inhibitor, a fibric acid derivative, an upregulator of LDL receptor activity, a lipoxygenase inhibitor, or an ACAT inhibitor; the antihypertensive agent is an ACE inhibitor, angiotensin II receptor antagonist, NEP/ACE inhibitor, calcium channel blocker and/or  $\beta$ -adrenergic blocker. --

--40. (Amended) The combination as defined in Claim 39 wherein the antidiabetic agent is 1, 2, 3 or more of metformin, glyburide, glimepiride, glipryide, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, troglitazone, rosiglitazone, insulin, GI-262570, isaglitazone, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinide, nateglinide, KAD1129, AR-HO39242, GW-409544, KRP297, AC2993, LY315902, P32/98 and/or NVP-DPP-728A; the anti-obesity agent is orlistat, ATL-962, AJ9677, L750355, CP331648, sibutramine, topiramate, axokine, dexamphetamine, phentermine, phenylpropanolamine, and/or mazindol; the lipid lowering agent is pravastatin, lovastatin, simvastatin, atorvastatin, cerivastatin, fluvastatin,

amlodipine besylate, prazosin HCl, verapamil, nifedipine, nadolol, propranolol, carvedilol, or clonidine HCl; the platelet aggregation inhibitor is aspirin, clopidogrel, ticlopidine, dipyridamole or ifetroban. --

**Please add the following Claims 55 and 56.**

55. A method for lowering blood glucose levels or for treating diabetes, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound which has the structure



(CH<sub>2</sub>)<sub>m</sub> is CH<sub>2</sub> or  $\begin{array}{c} \text{CH}_3 \\ | \\ \text{---CH---} \end{array}$  and R<sup>3</sup> is aryloxy carbonyl or alkoxyaryloxy carbonyl.



56. The method as defined in Claim 55 where in the compound employed  $(CH_2)_m$  is  $CH_2$ .

REMARKS

Claims 2 to 5, 10, 14, 16 to 18, 20 to 22, 26 to 28, 31, 34, 37, 39, 40, 50, 55 and 56 are present.

The invention in this application involves method of use claims 34, 36 and pharmaceutical combination Claim 37 and claims dependents thereon. These claims have been divided out of parent application Serial No. 09/812,960, now allowed.

The addition of  $R^3$  as polyhaloalkylaryloxycarbonyl in Claim 1 is based on original Claim 10, lines 29-30.

Claims 34 to 37 have been combined.

Claims 39, 42, 44 and 47 have been combined.

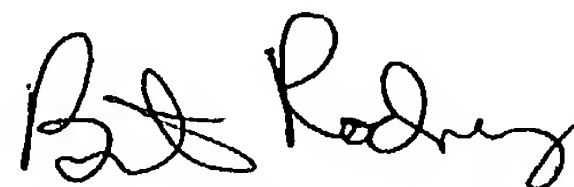
Claims 40, 43, 45, 48 and 49 have been combined.

Claims 50 and 51 have been combined.

The compounds claimed in the method of use and pharmaceutical combination claims are those which have been allowed in parent application Serial No. 09/812,960. Accordingly, it is submitted that the methods of use and combinations claimed herein which include the compounds allowed in parent application Serial No. 09/812,960 are patentable as well.

Accordingly., it is submitted that Claims 2 to 5, 10, 14, 16 to 18, 20 to 22, 26 to 28, 31, 32, 34, and 36 to 56 are patentable for the same reasons that the compounds of parent application Serial No. 09/812, 960 have been deemed patentable. Thus, it is believed that the above claims are in condition for allowance.

Respectfully submitted,



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Reg. No. 22,076

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Patent Department  
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Date:

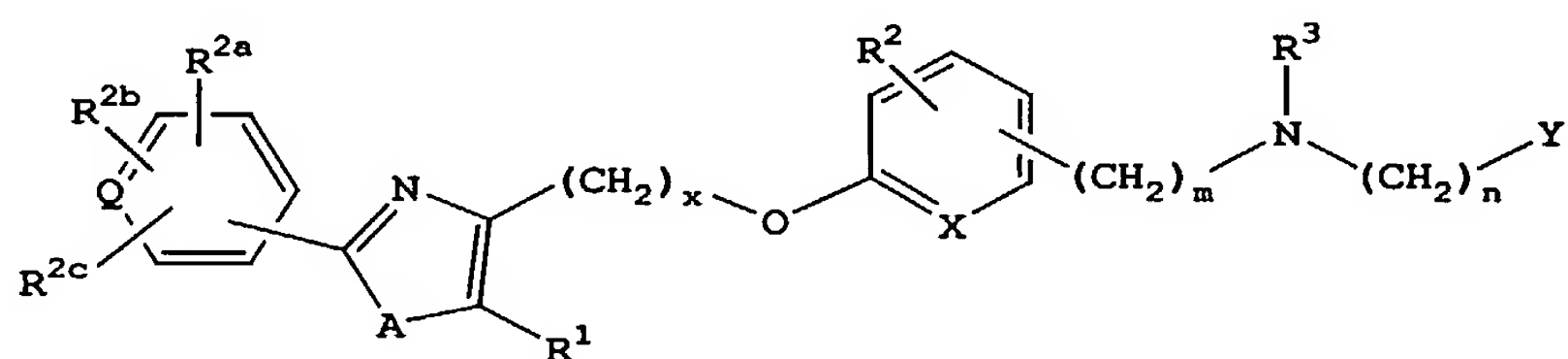
2/22/02

VERSION WITH MARKINGS TO SHOW CHANGES MADE

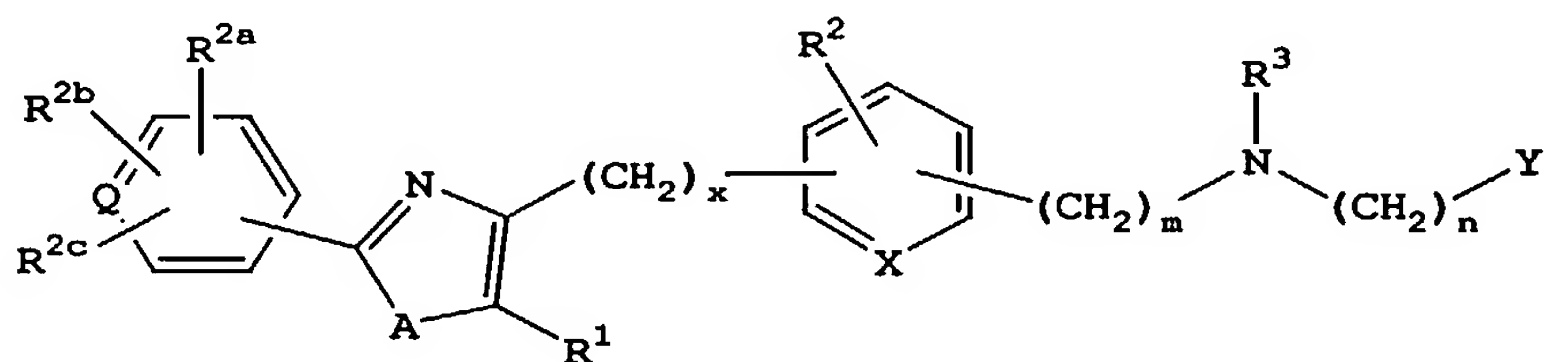
Please cancel Claims 1, 6 to 9, 11 to 13, 15, 19, 23 to 25, 29, 33 and 35.

Please amend Claims 2 to 5, 10, 14, 16 to 18, 20 to 22, 26 to 28, 30 to 32, 34, 36 and 37 as follows.

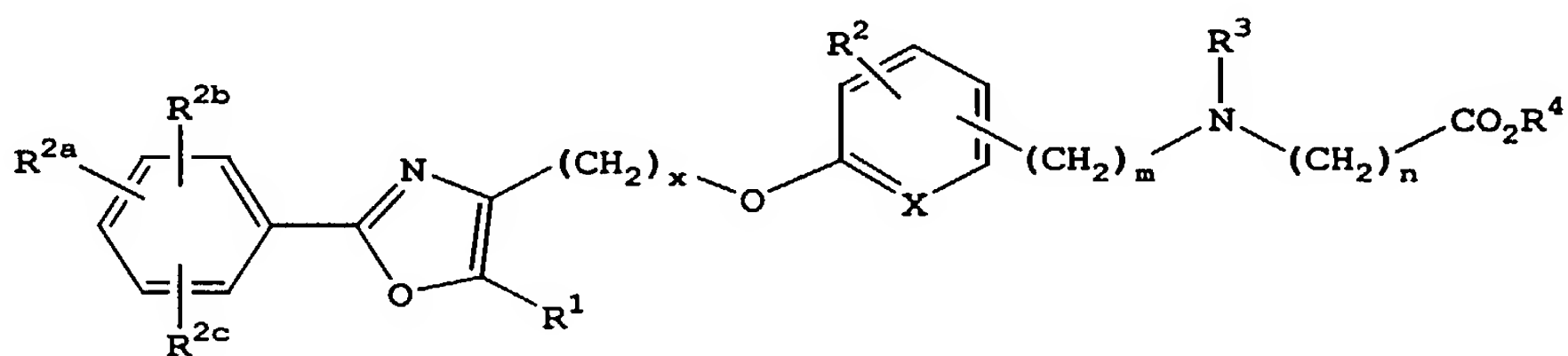
--2. (Amended) The method as defined in Claim 34 wherein the [A] compound [having] employed has the structure



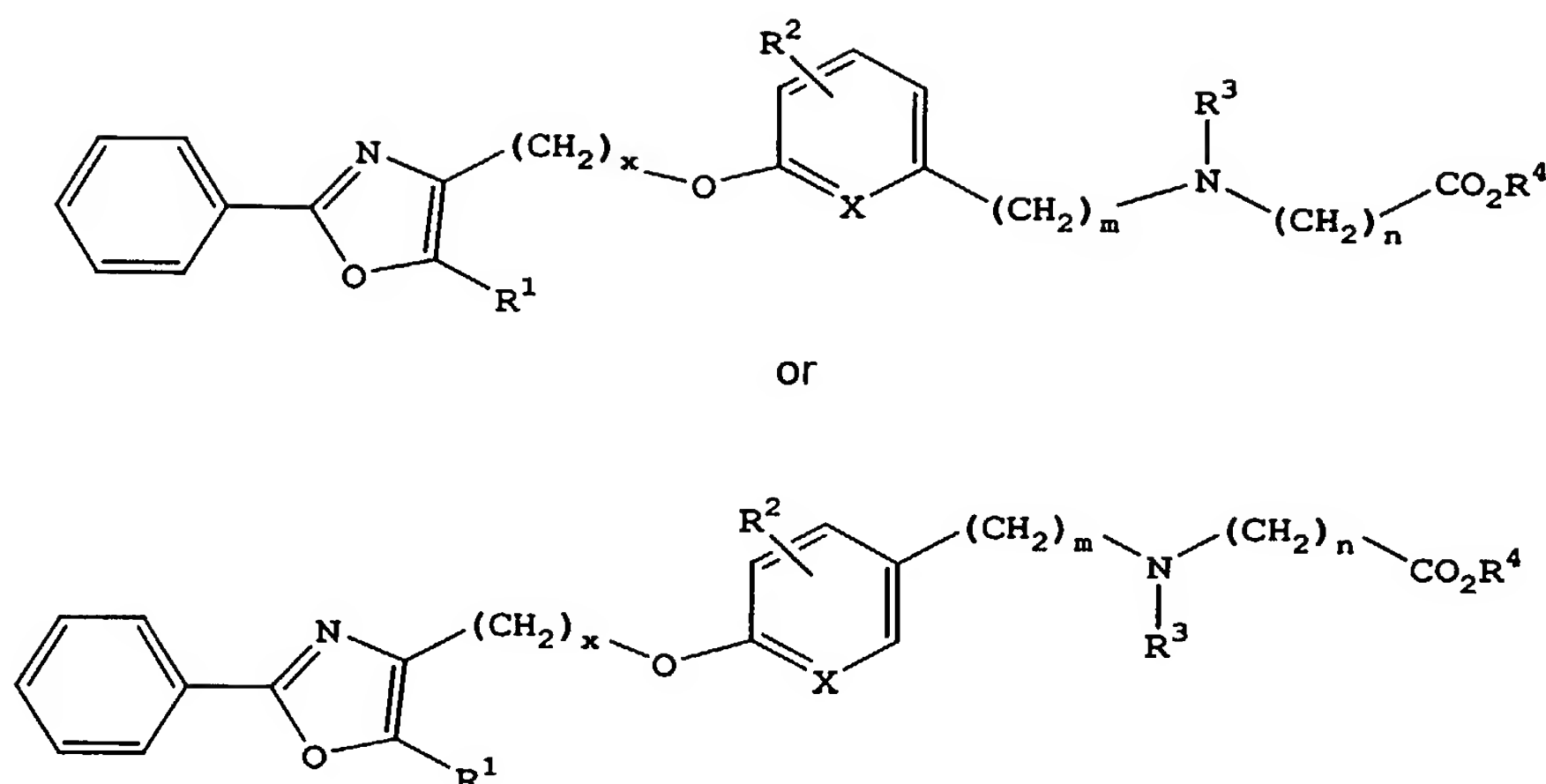
or



--3. (Amended) The [compound] method as defined in Claim [1] 34 wherein the compound employed has the [having the] structure



--4. (Amended) The [compound] method as defined in Claim [1] 34 wherein the compound employed has the [having the] structure

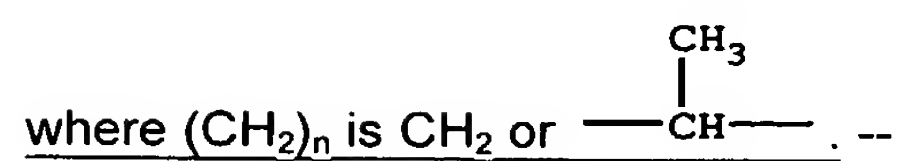


--5. (Amended) The [compound] method as defined in Claim [1] 34 where in the compound employed [wherein]  $(CH_2)_x$  is alkylene, alkenylene, allenyl, or alkynylene. --

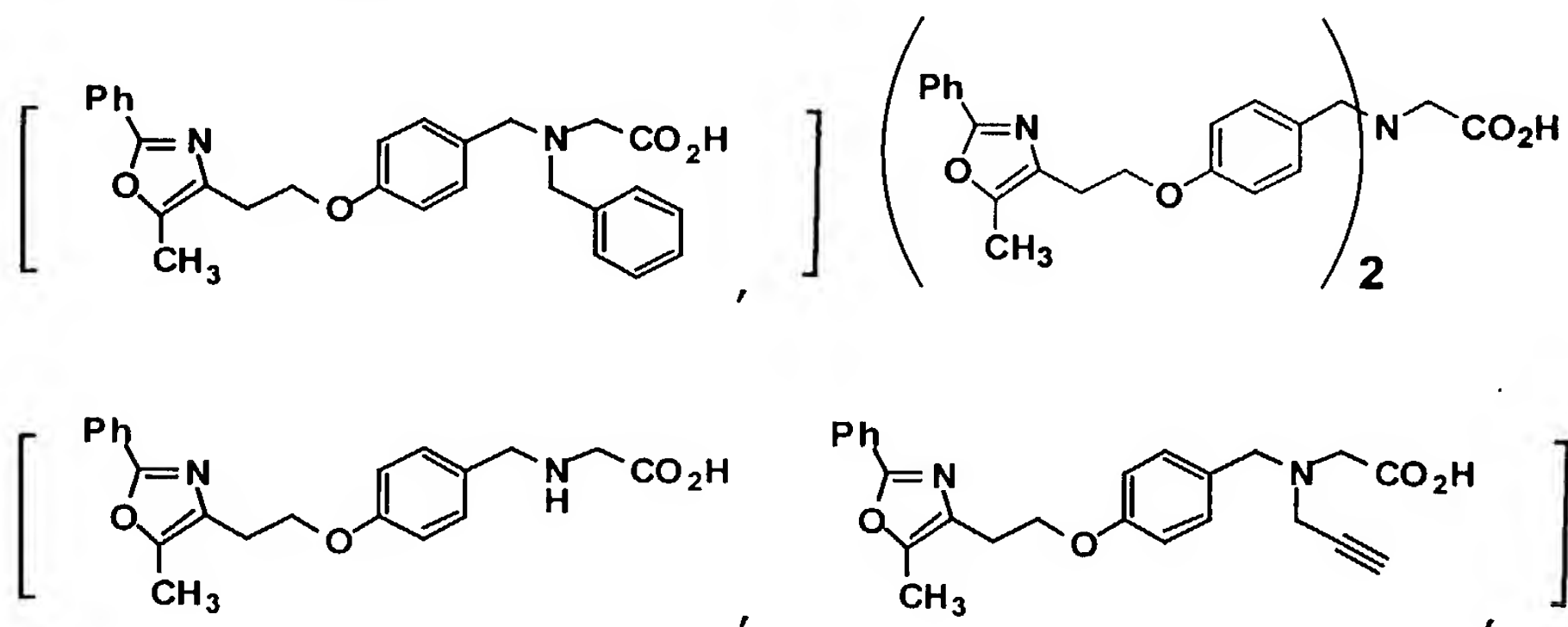
--10. (Amended) The [compound] method as defined in Claim [1] 34 [wherein  $R^{2a}$  is alkoxy or H,] where in the compound employed

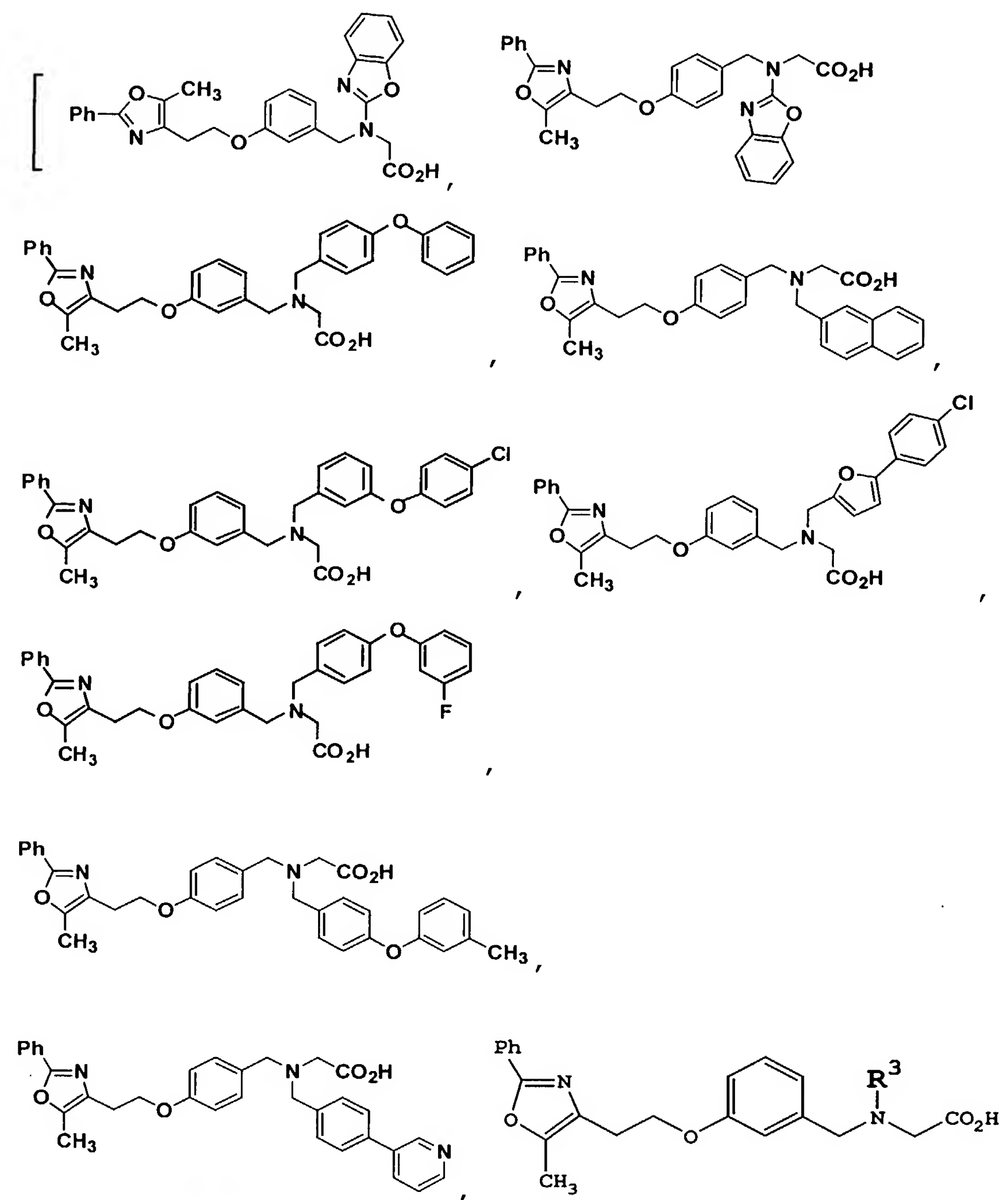
$(CH_2)_x$  is  $CH_2$ ,  $(CH_2)_2$ ,  $(CH_2)_3$ , or  $\begin{array}{c} CH_3 \\ | \\ C \\ | \\ CH_3 \end{array}$ ,  $(CH_2)_m$  is  $CH_2$ , or  $\begin{array}{c} R_a \\ | \\ CH \end{array}$  [(]where  $R_a$  is alkyl or alkenyl[)],  $(CH_2)_n$  is  $CH_2$ ,  $R^1$  is lower alkyl, [preferably  $-CH_3$ ,]  $R^2$  is H,  $R^{2a}$  is H,  $R^4$  is H, [X is CH,] and  $R^3$  is arylalkyloxycarbonyl, [arylheteroarylalkyl, aryloxyarylalkyl, arylalkyl,] aryloxycarbonyl, haloaryl-oxycarbonyl, alkoxyaryloxycarbonyl, alkylaryloxycarbonyl, aryloxyaryloxycarbonyl, heteroaryloxyarylalkyl, heteroaryloxycarbonyl, [aryloxyarylcarbonyl,] arylalkenyloxycarbonyl, cycloalkylaryloxycarbonyl, [arylalkylarylcarbonyl, heteroaryl-heteroarylalkyl,] cycloalkyloxyaryloxycarbonyl, [heteroaryl-heteroarylcarbonyl,] alkyloxyaryloxycarbonyl, arylalkylsulfonyl, arylalkenylsulfonyl, [alkoxyarylalkyl,] arylthiocarbonyl, cycloheteroalkylalkyloxycarbonyl, cycloheteroalkyloxycarbonyl, or polyhaloalkylaryloxycarbonyl, which may be optionally substituted.--

--14. (Amended) The [compound] method as defined in Claim [1] 34 wherein the compound employed has the [having the] structure



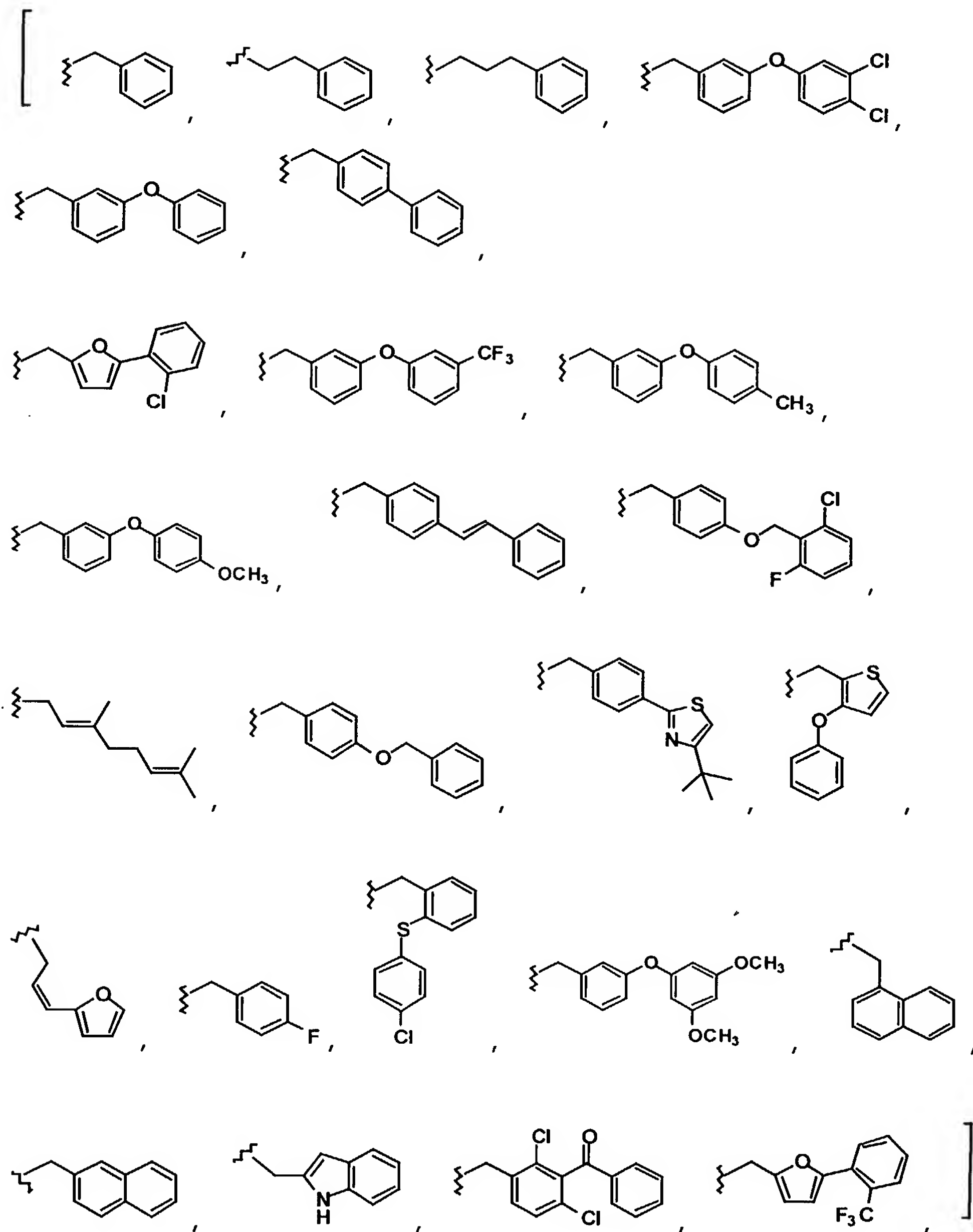
--16. (Amended) The [compound] method as defined in Claim [1 having] 34 wherein the compound employed has the structure

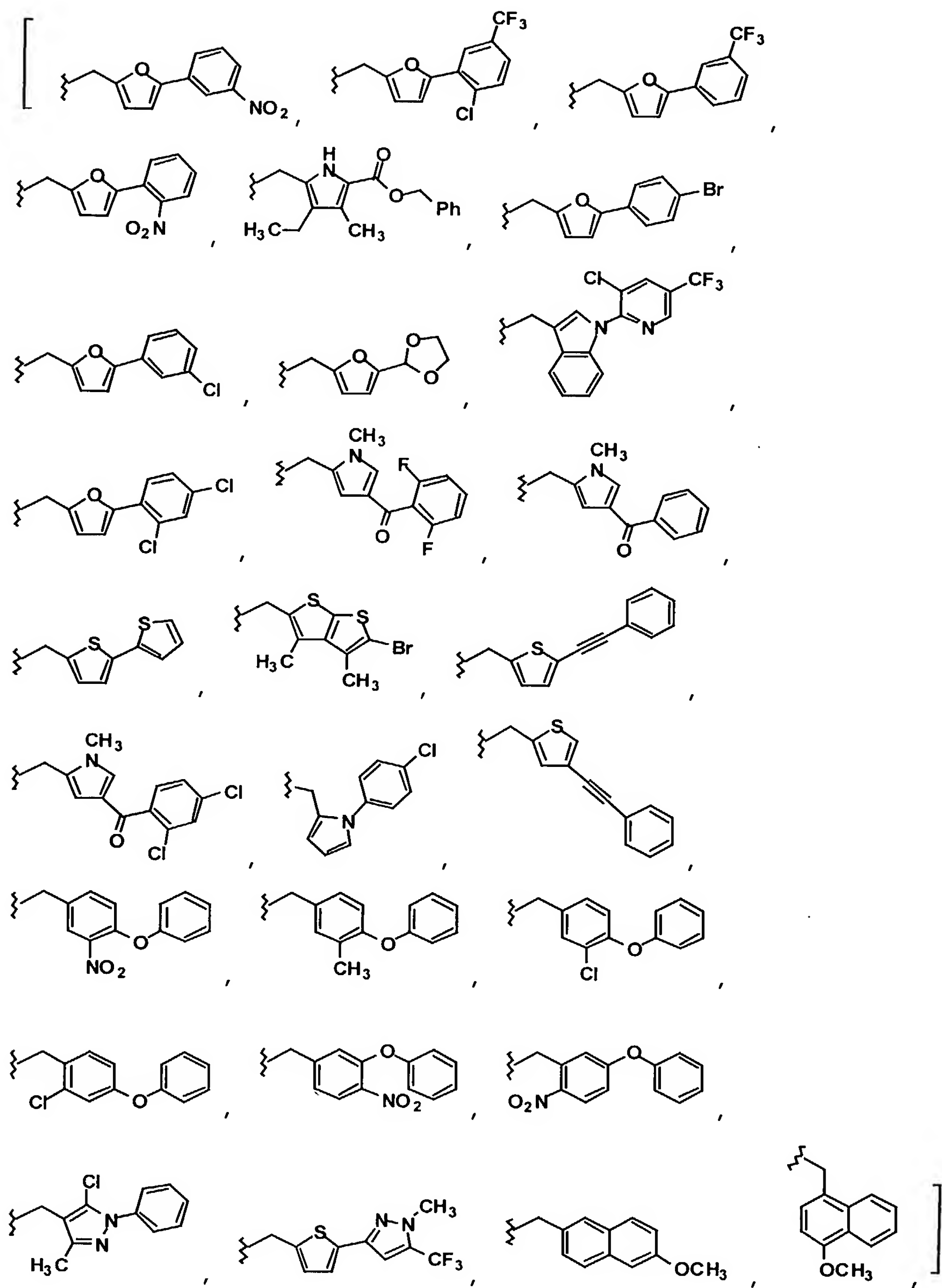


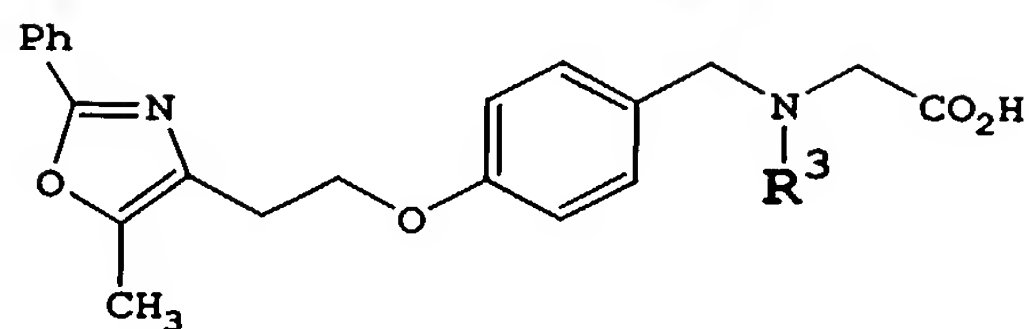
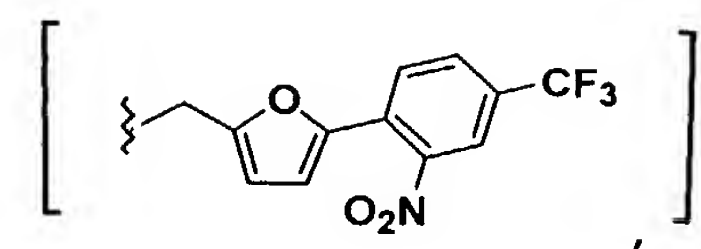


where  $R^3 =$  ]

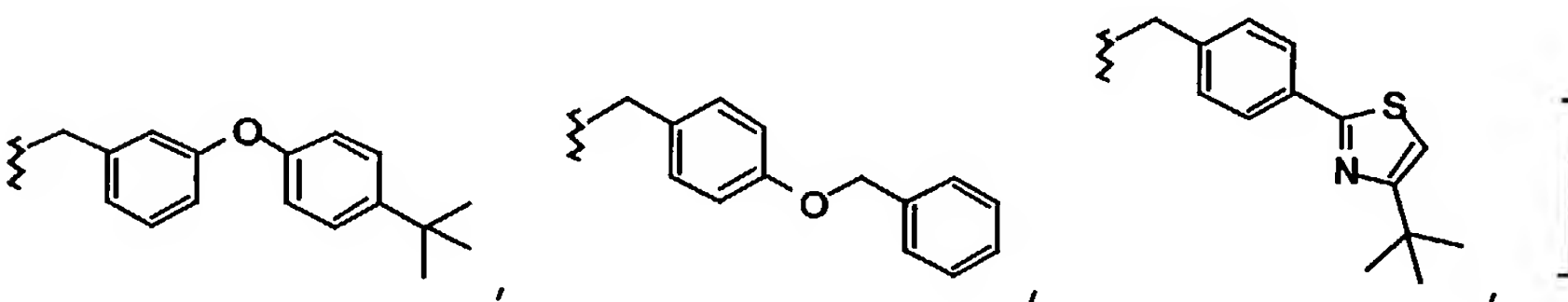
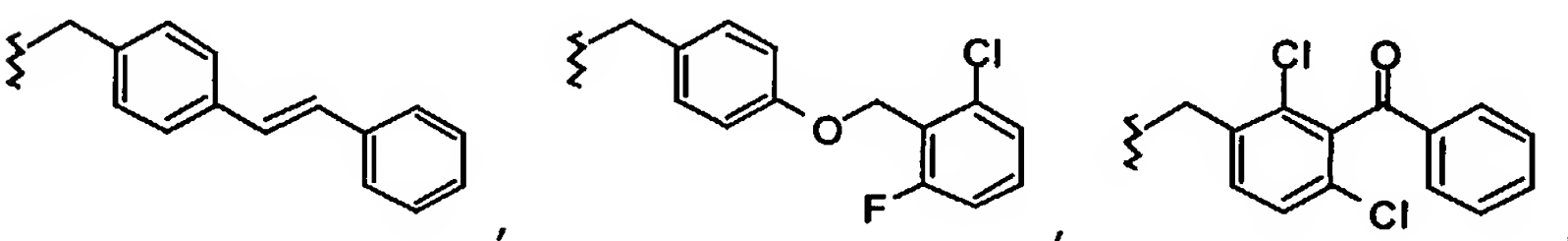
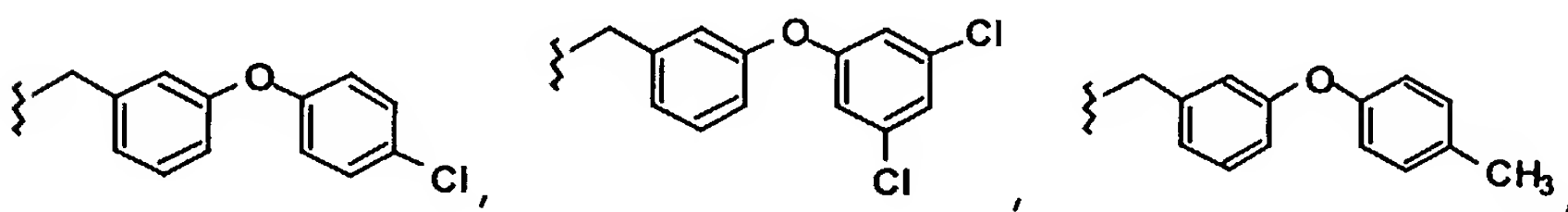
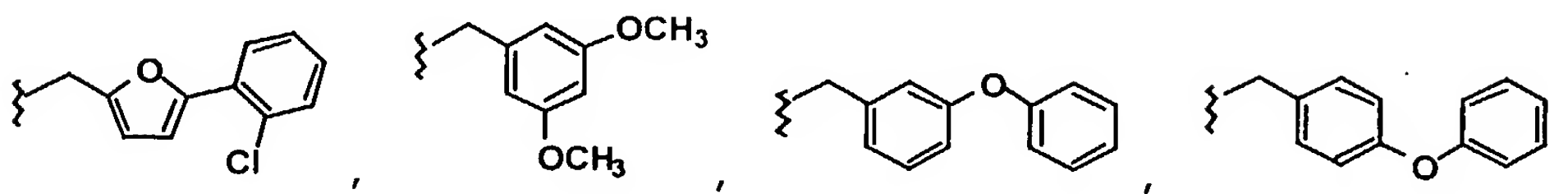
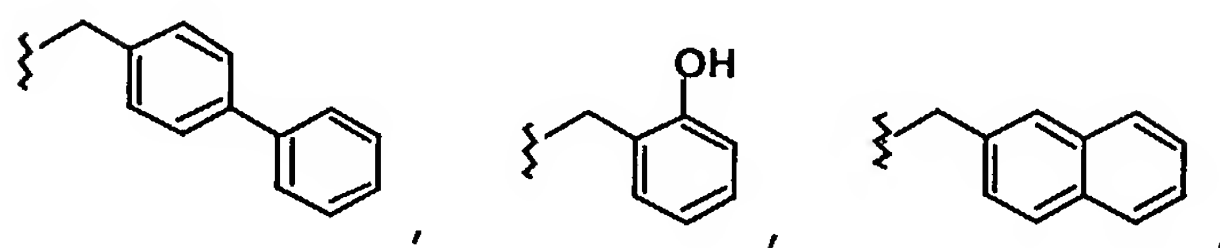
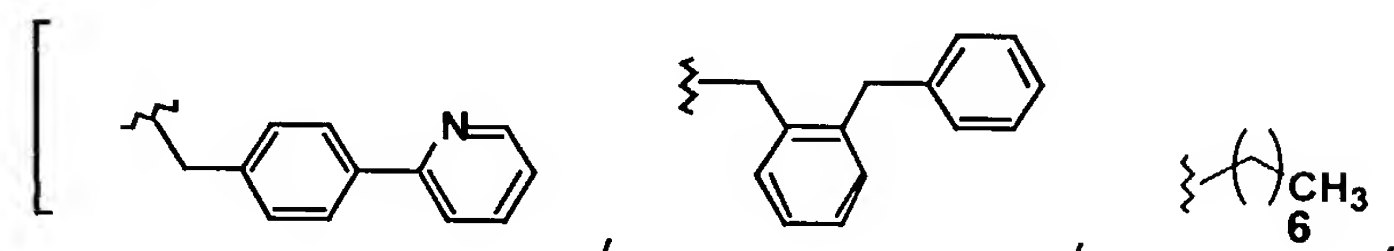
[  $R^3$  ]



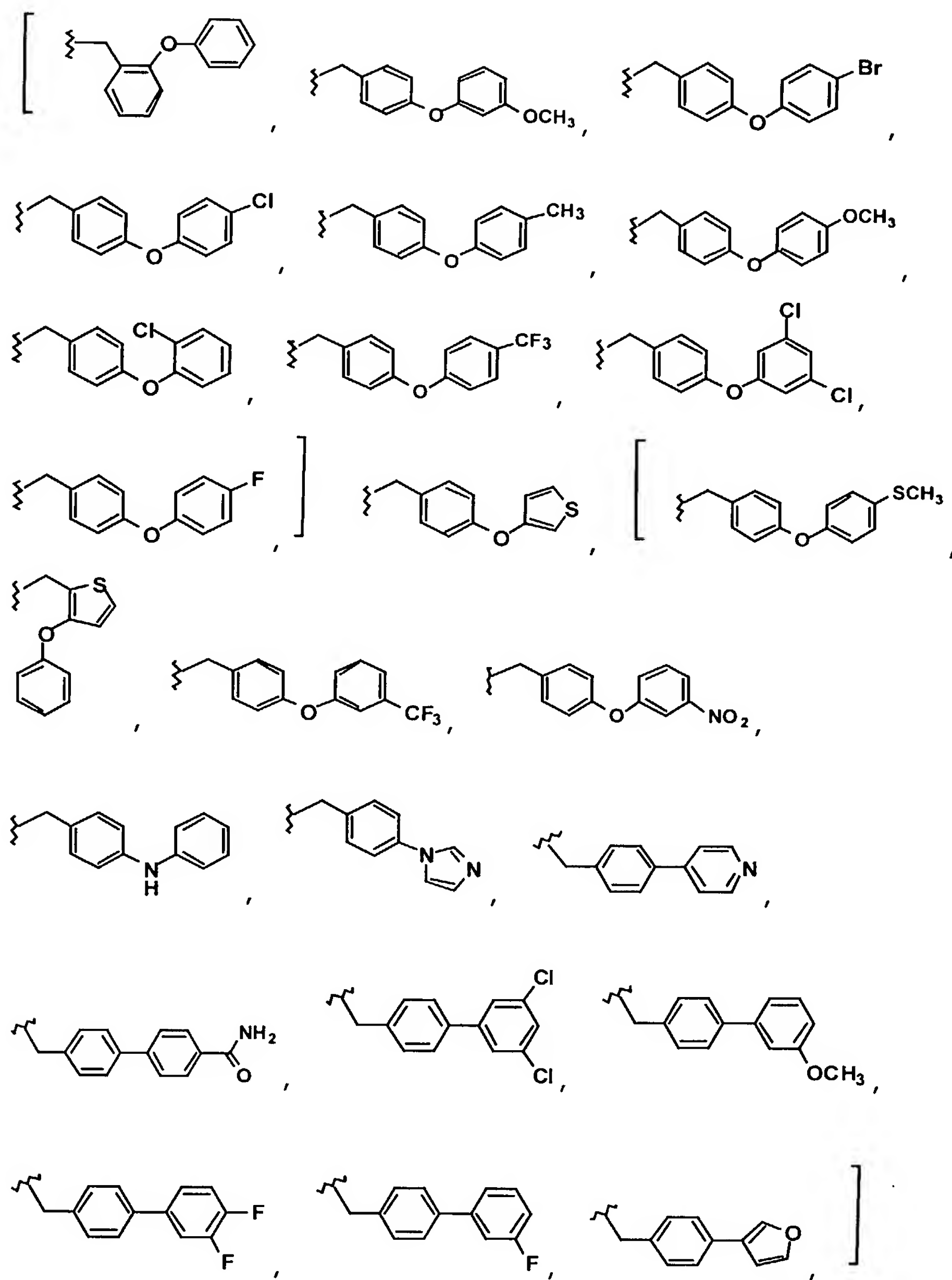


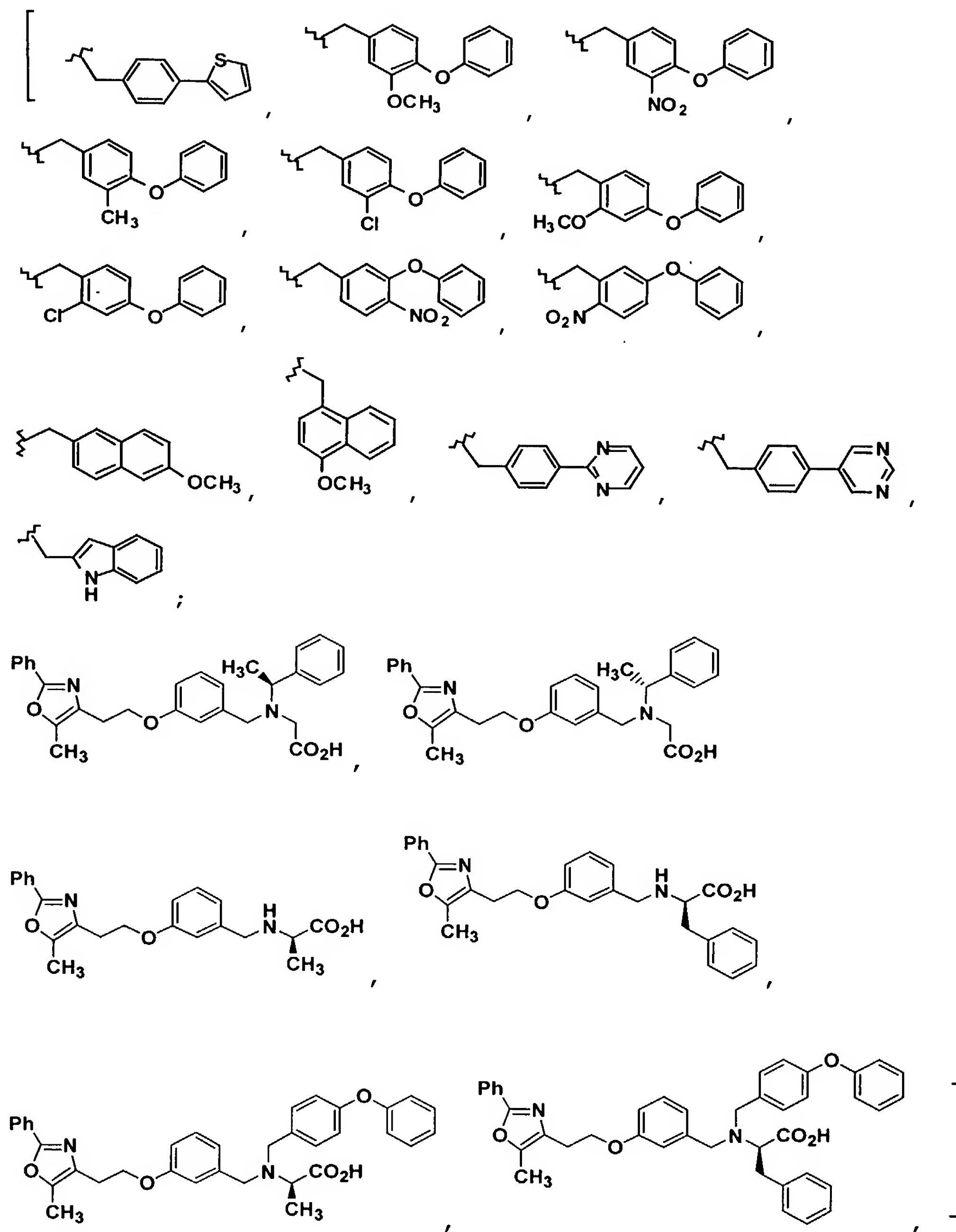


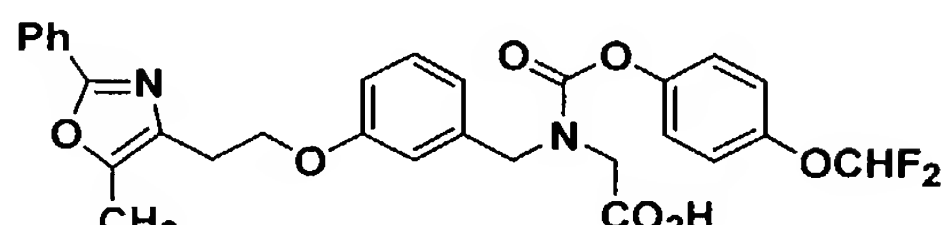
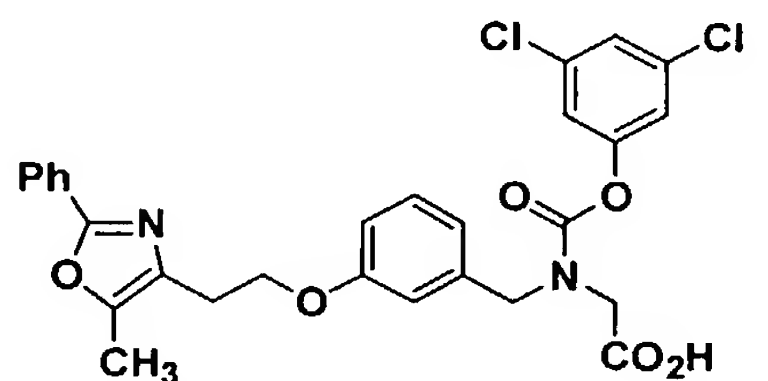
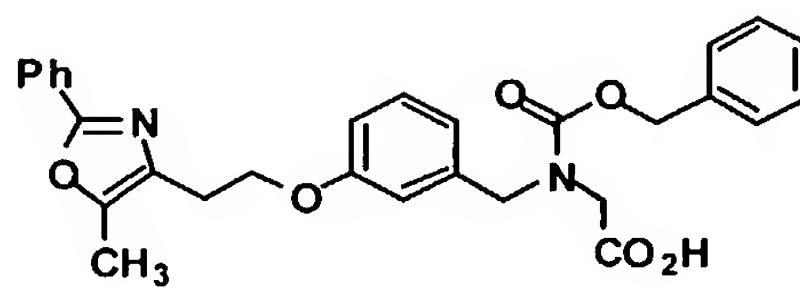
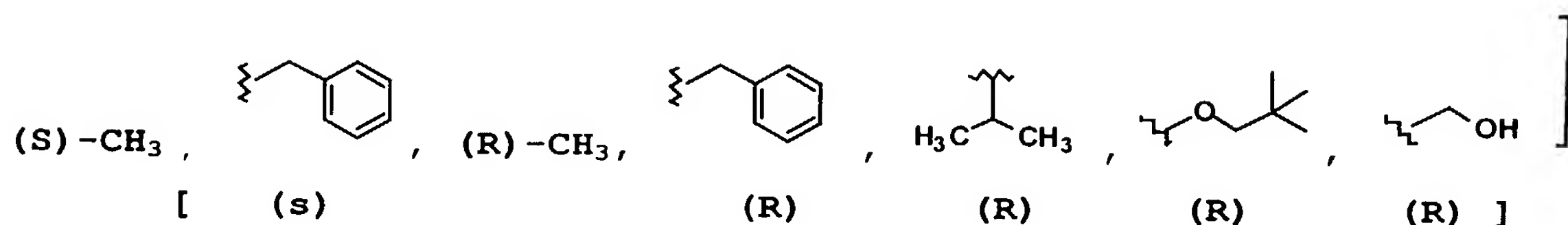
, where  $\text{R}^3 =$

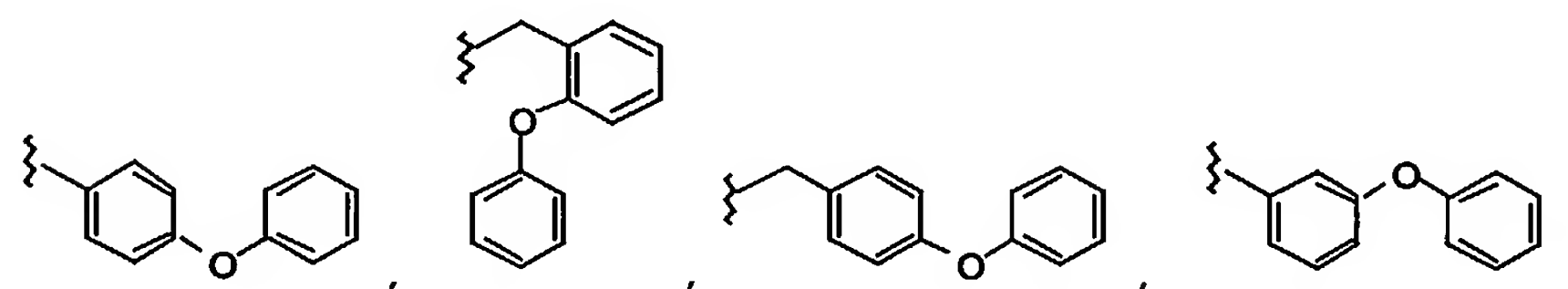


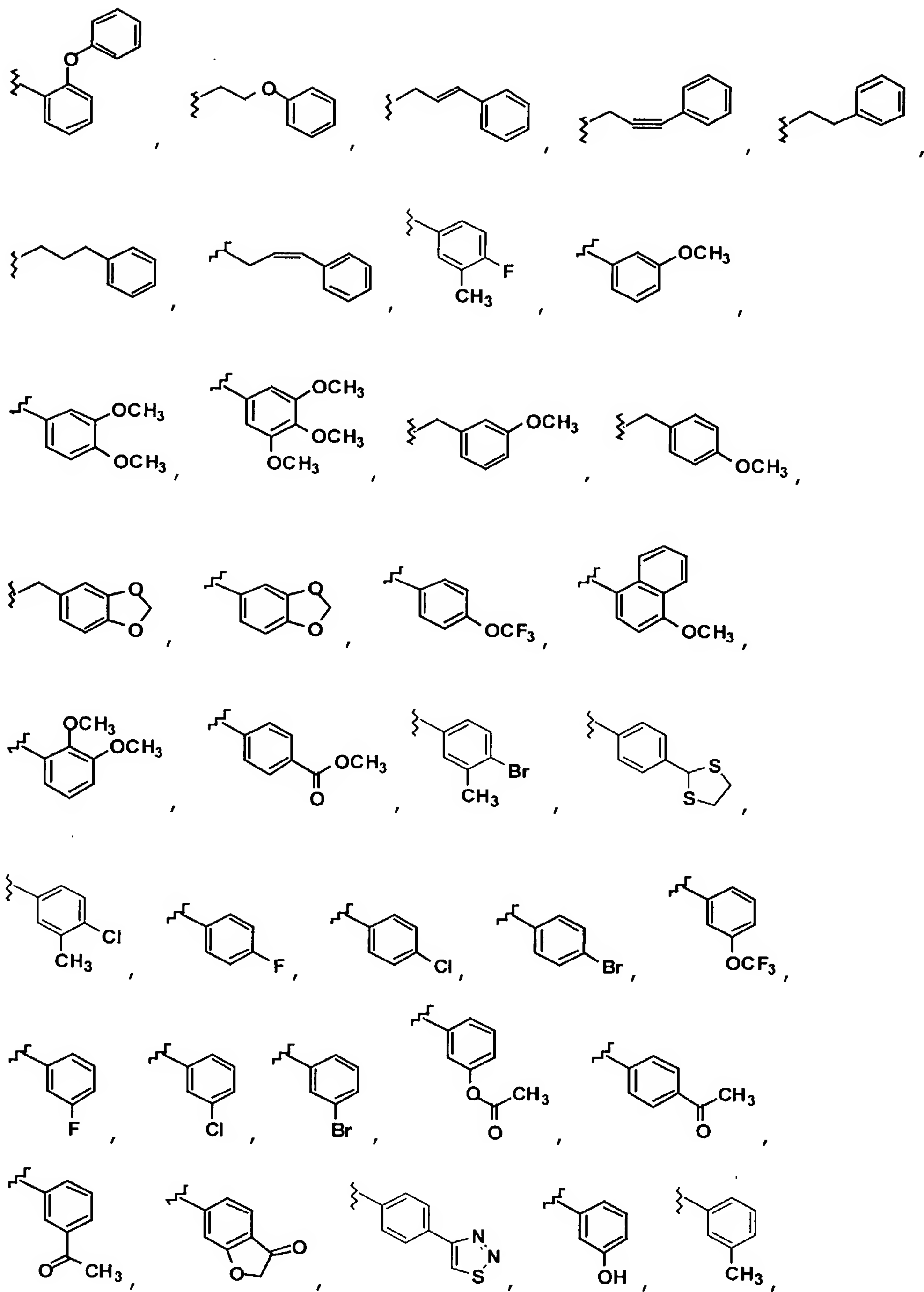


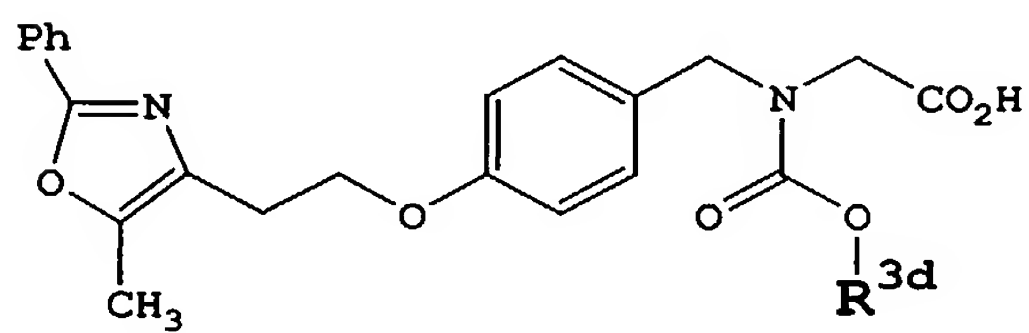
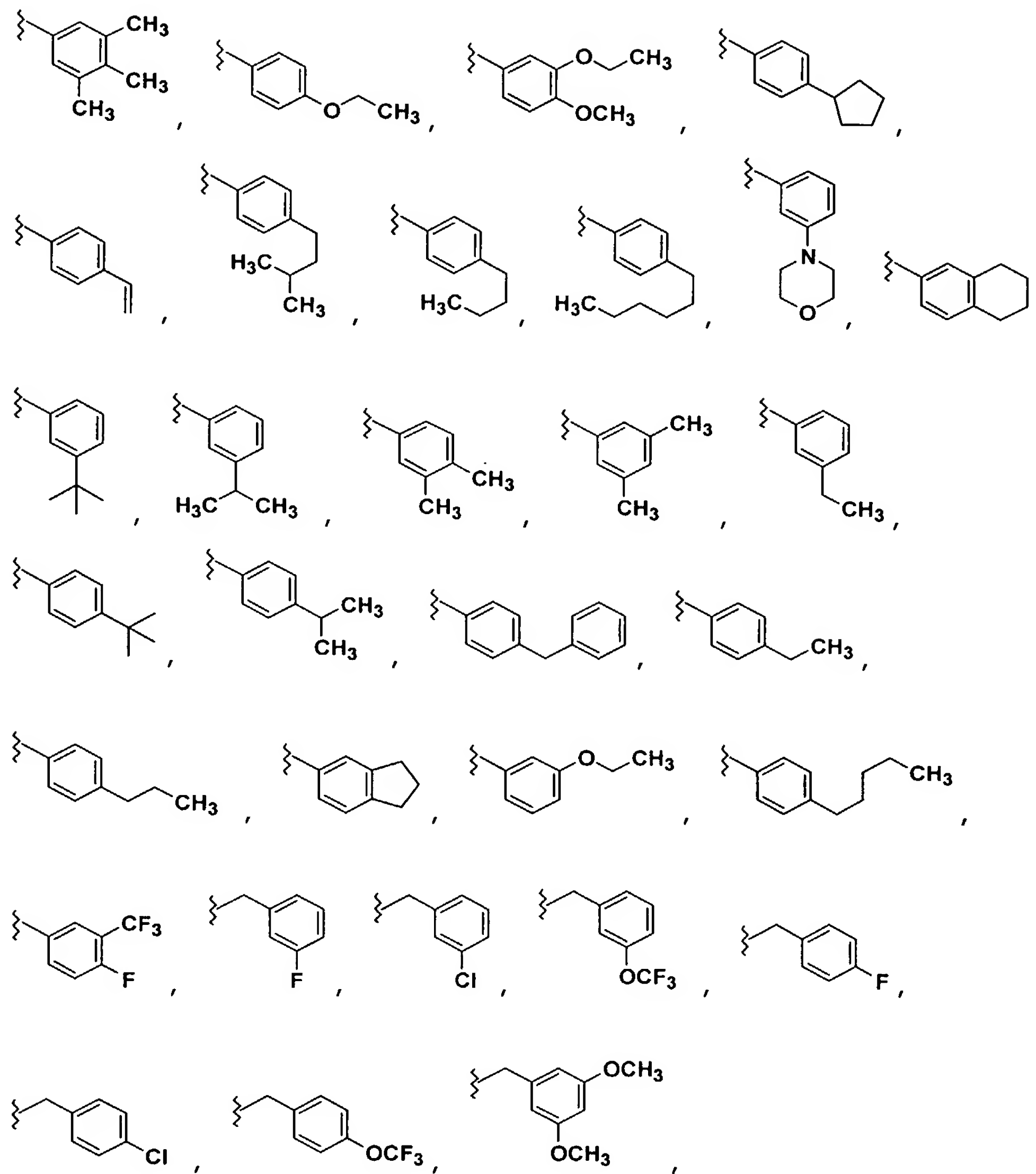




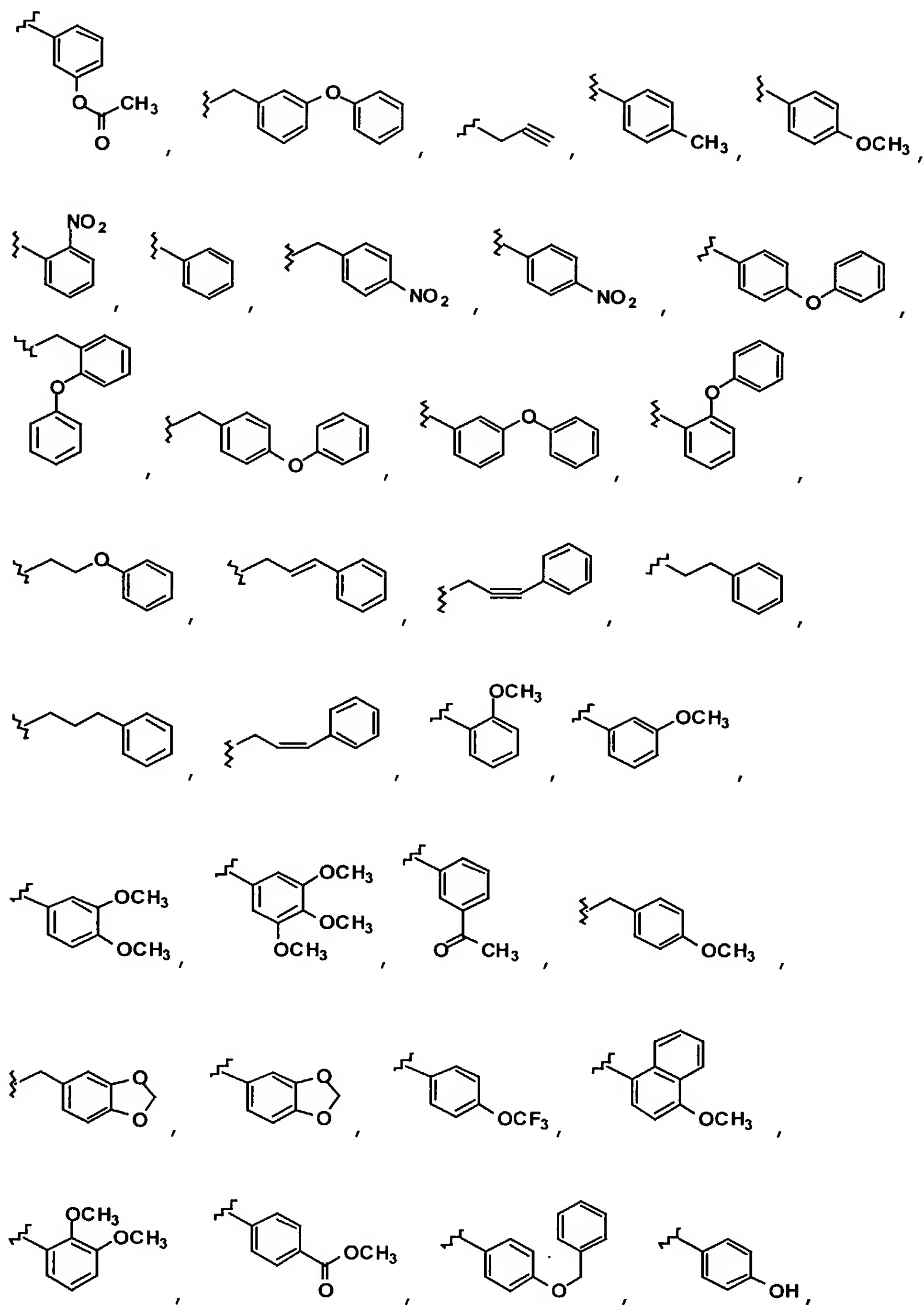


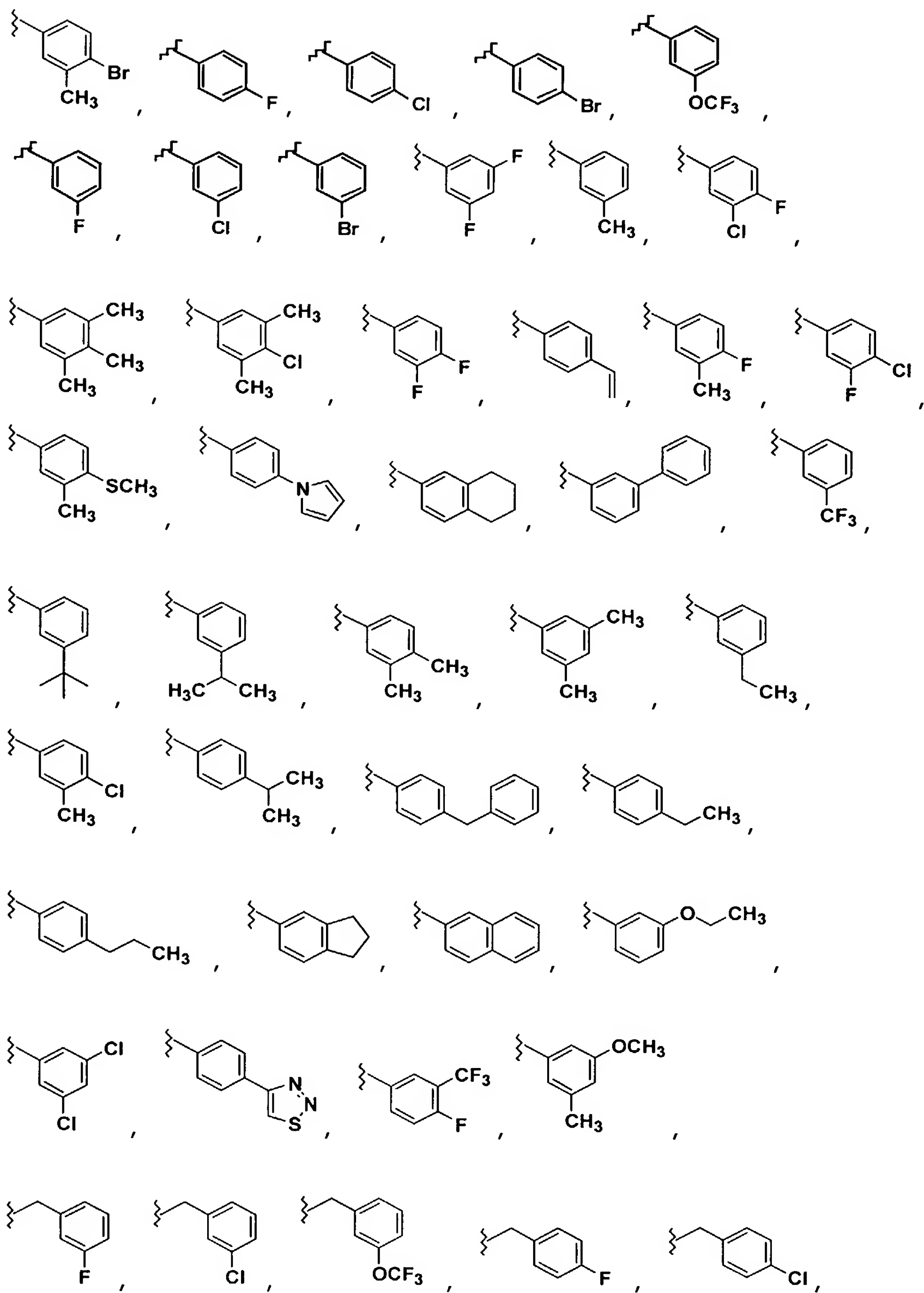




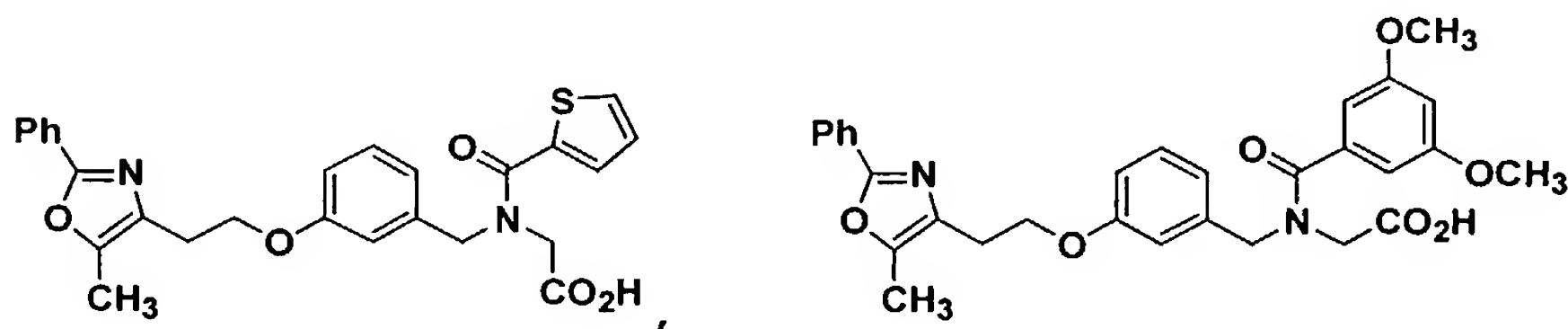
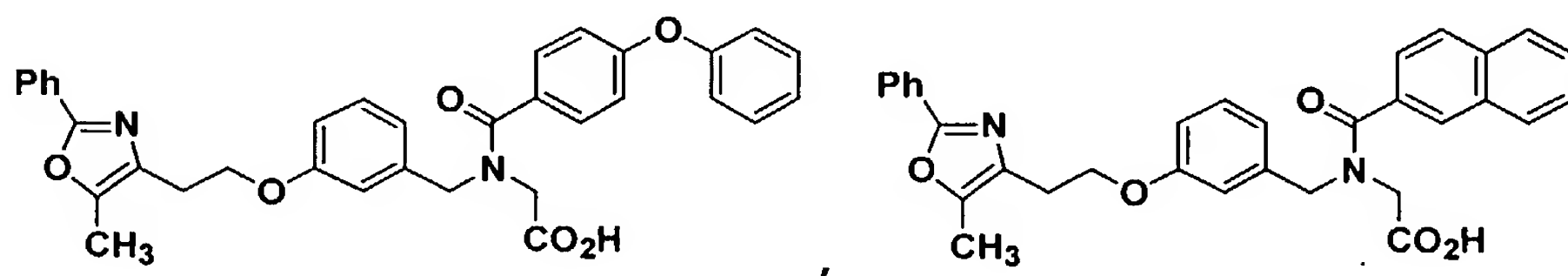
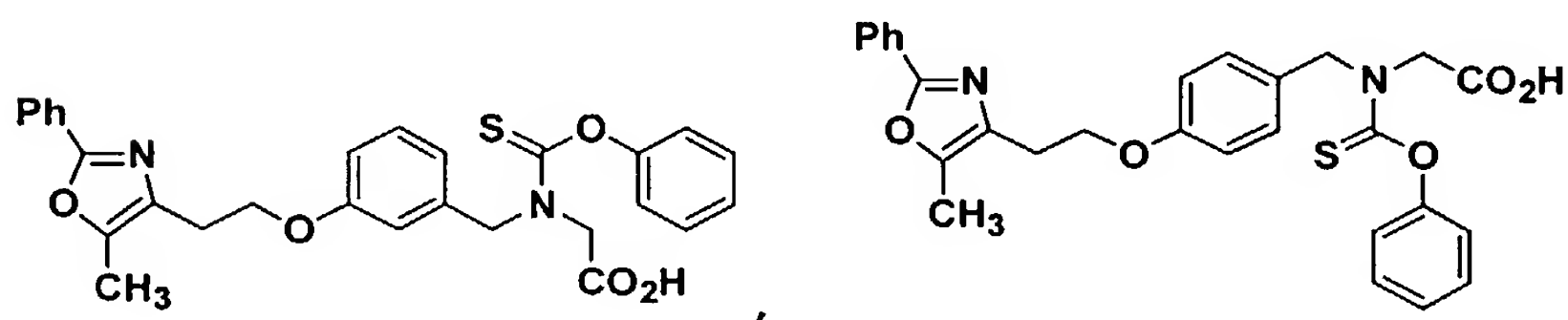
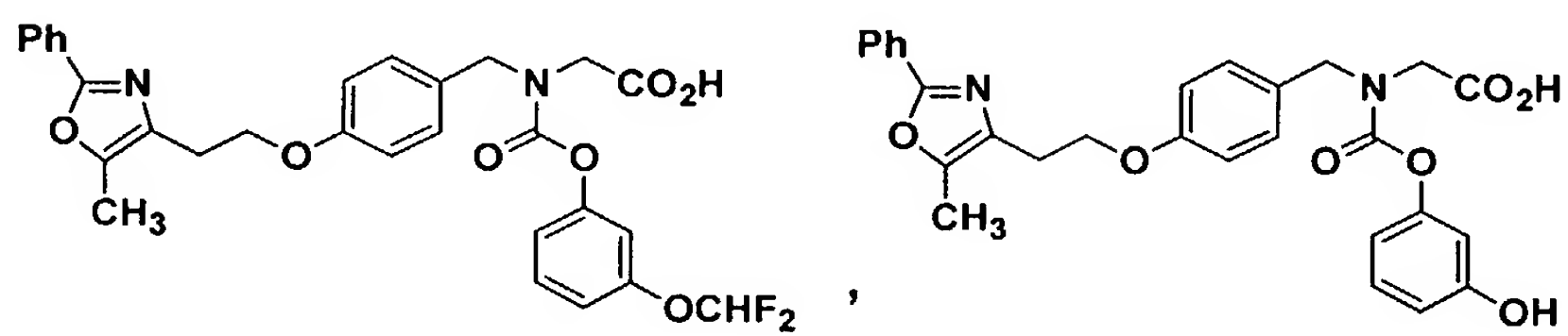
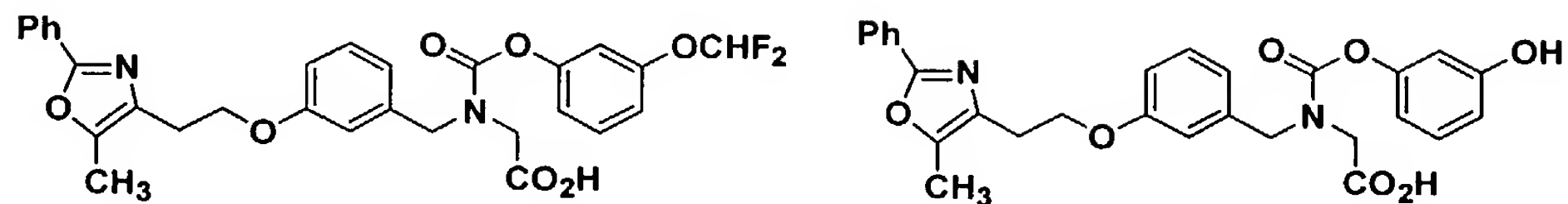
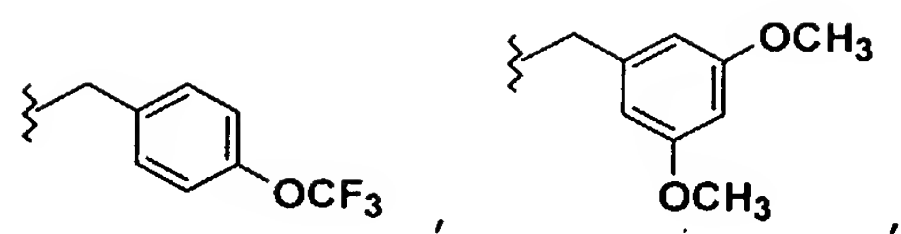


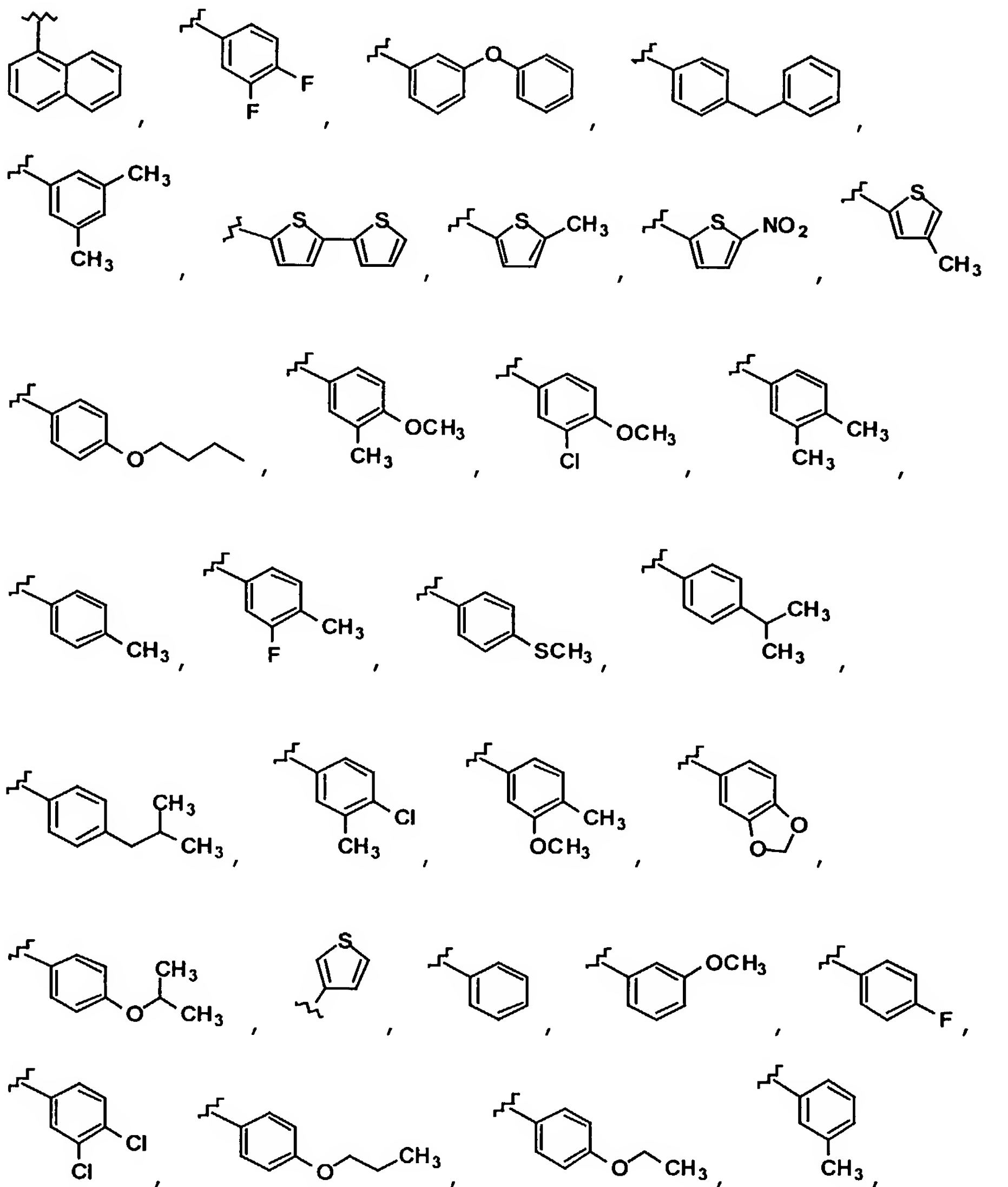
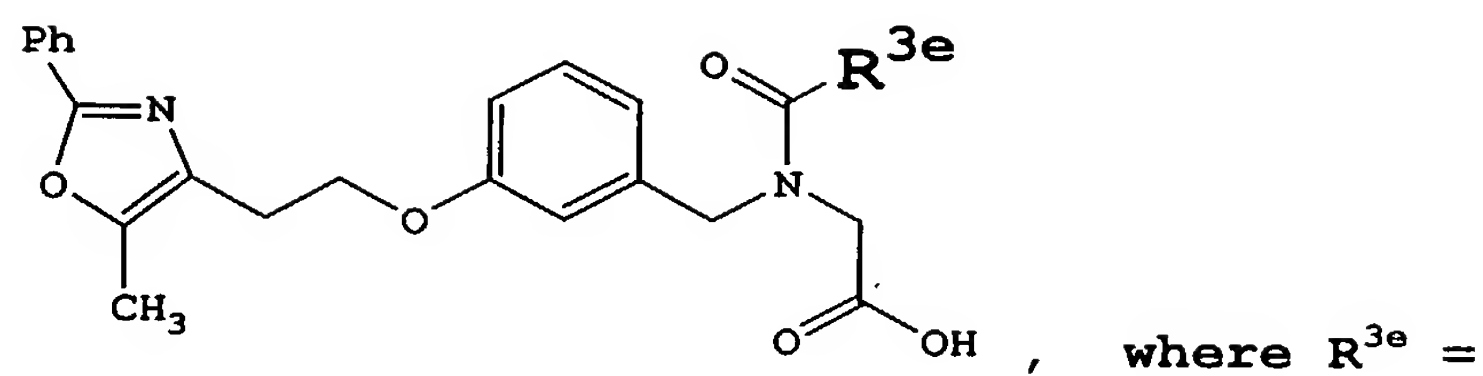
, where  $R^{3d} =$

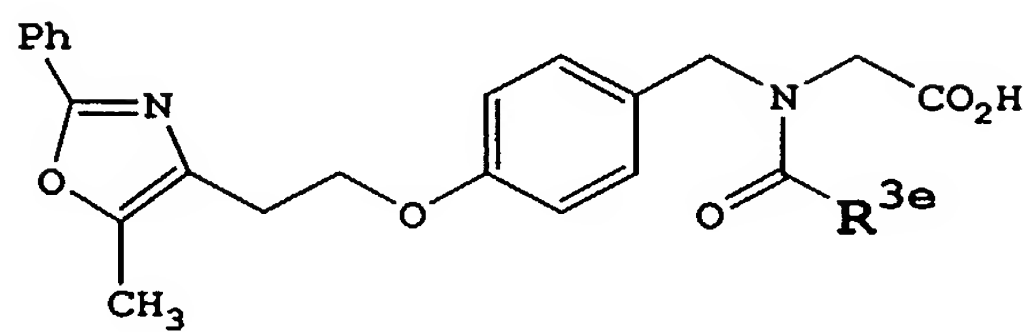
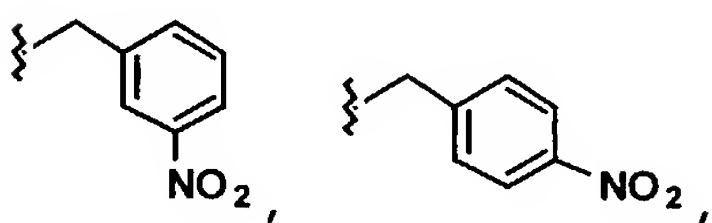
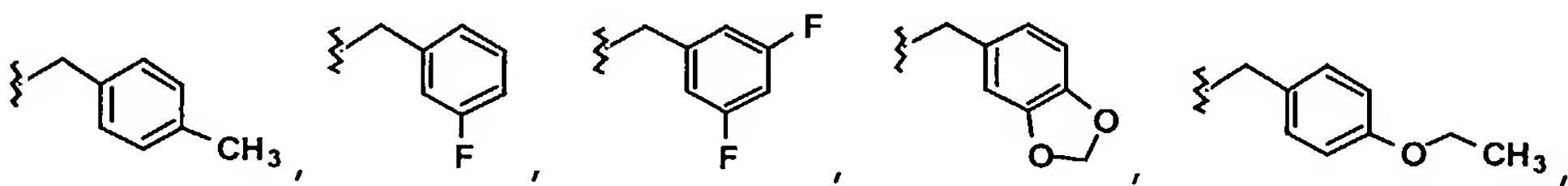
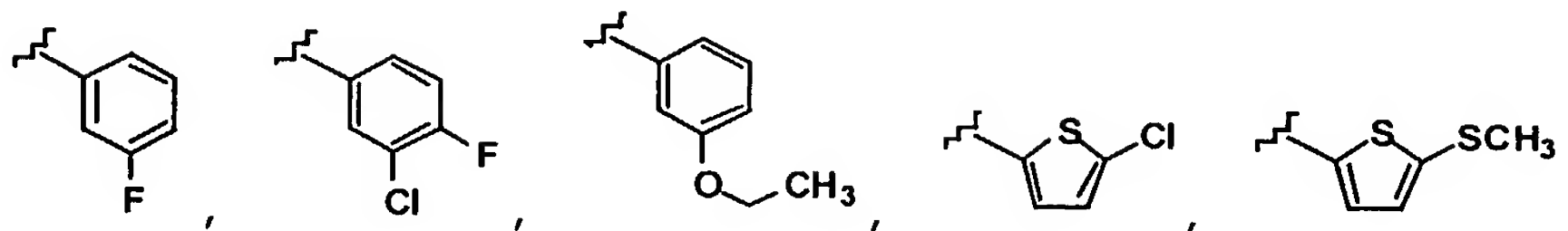
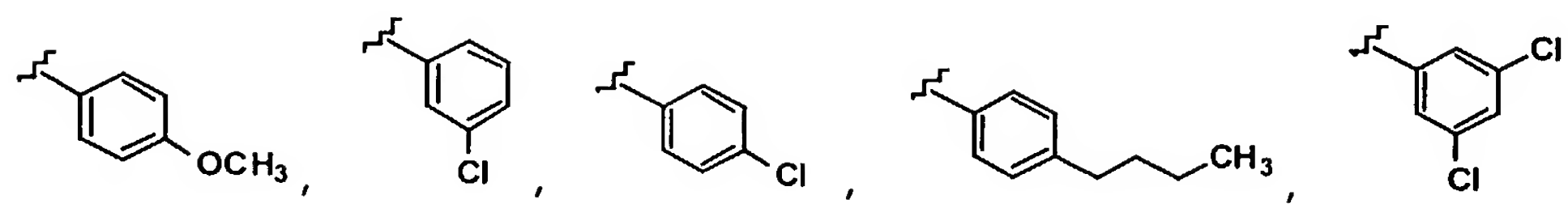




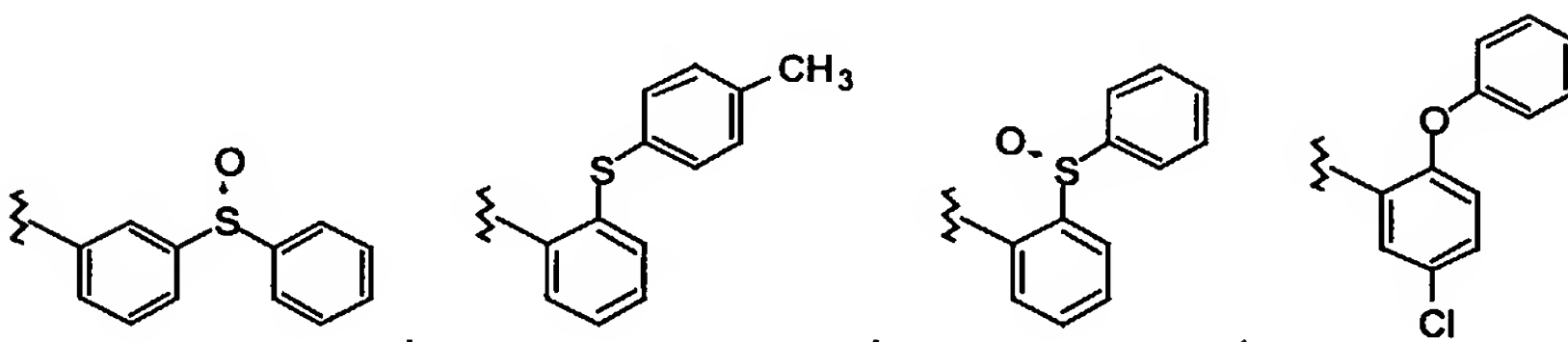
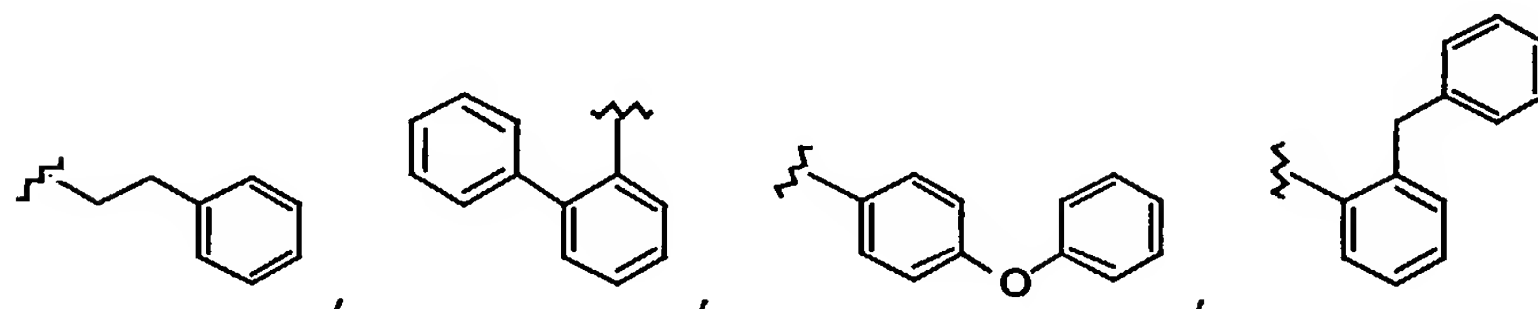


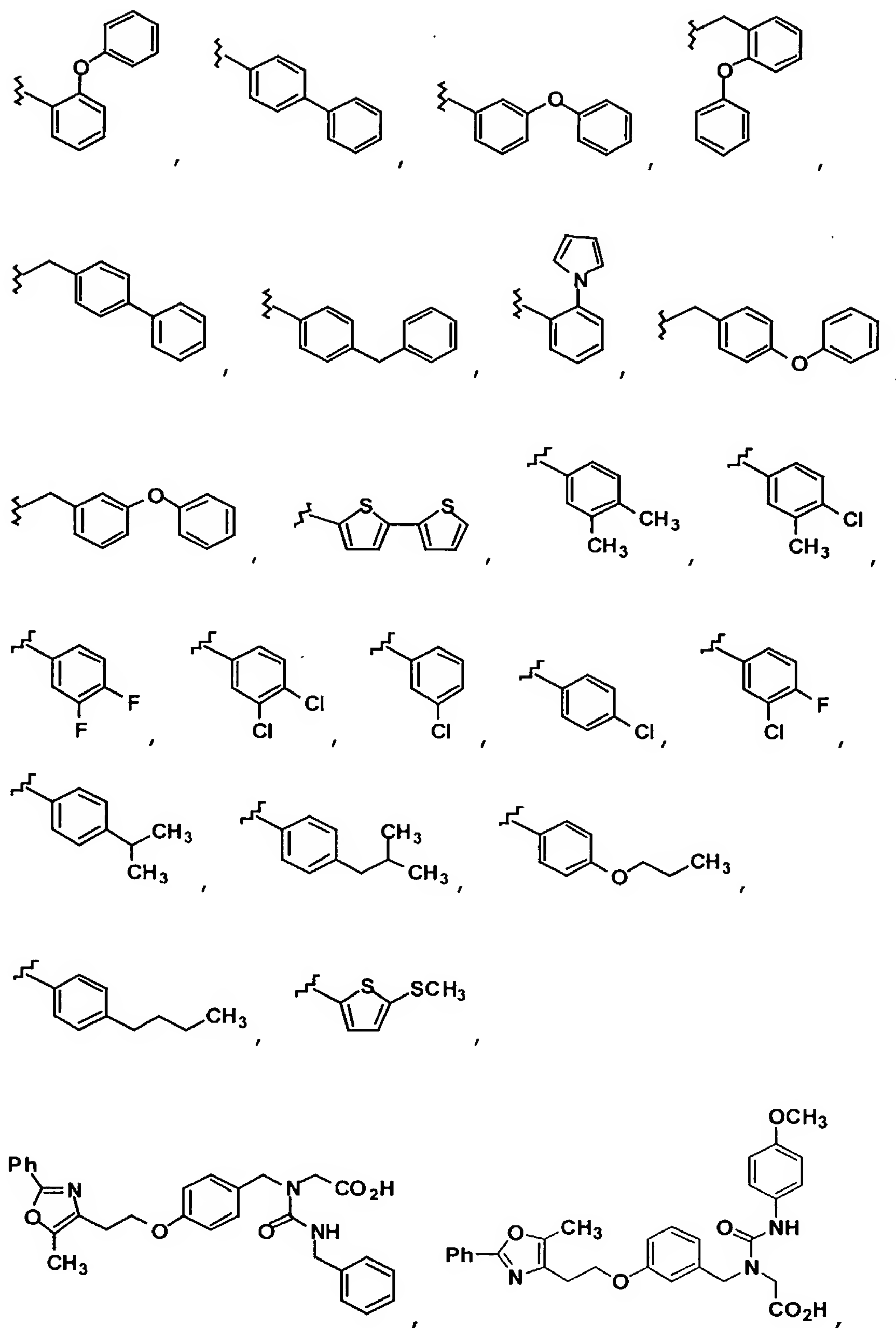


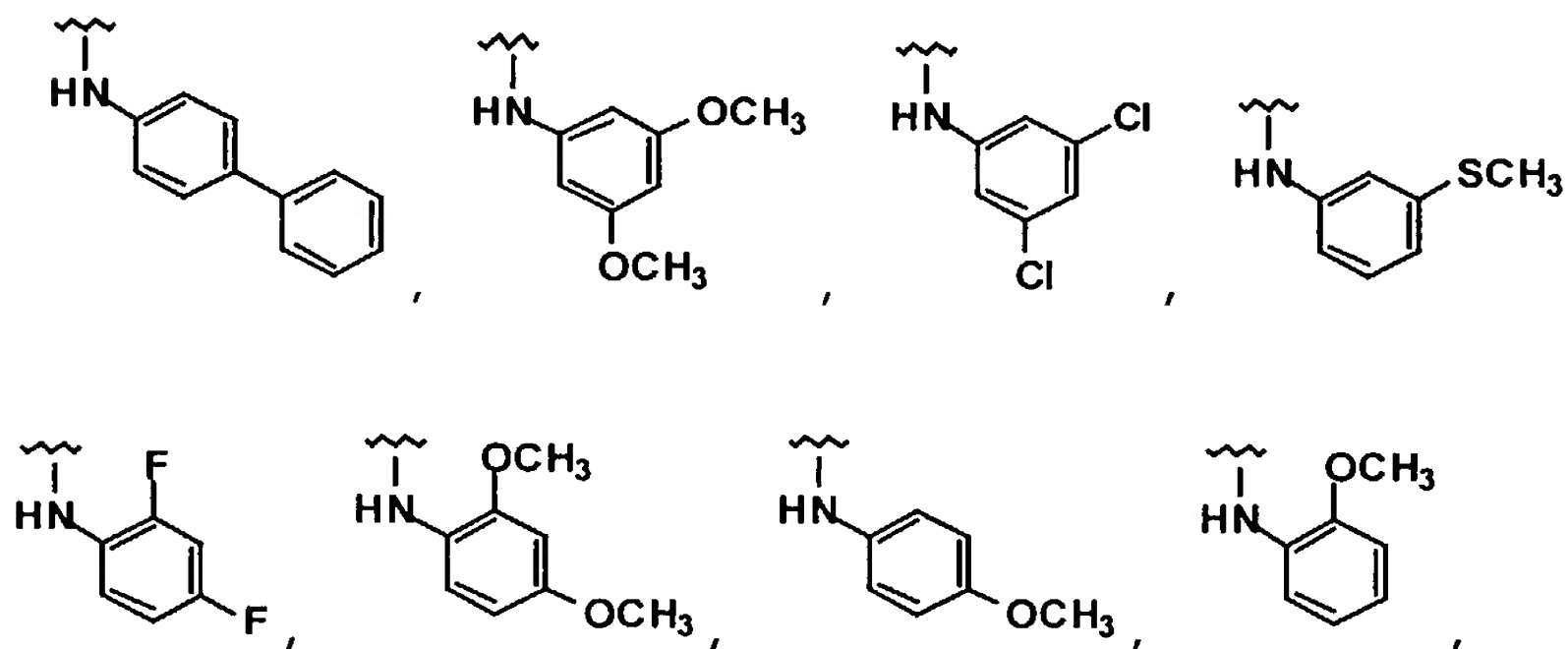
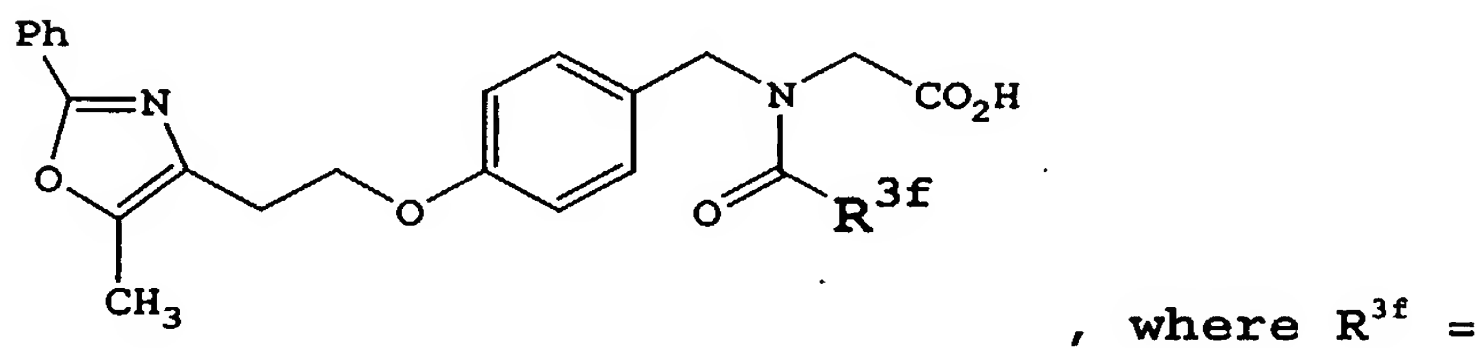
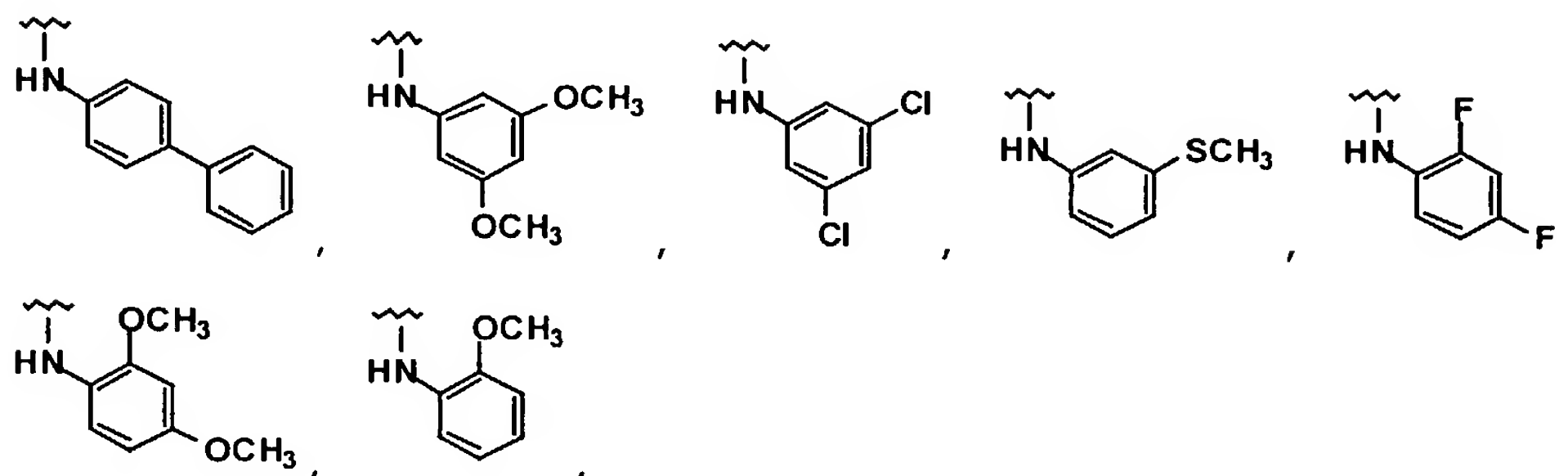
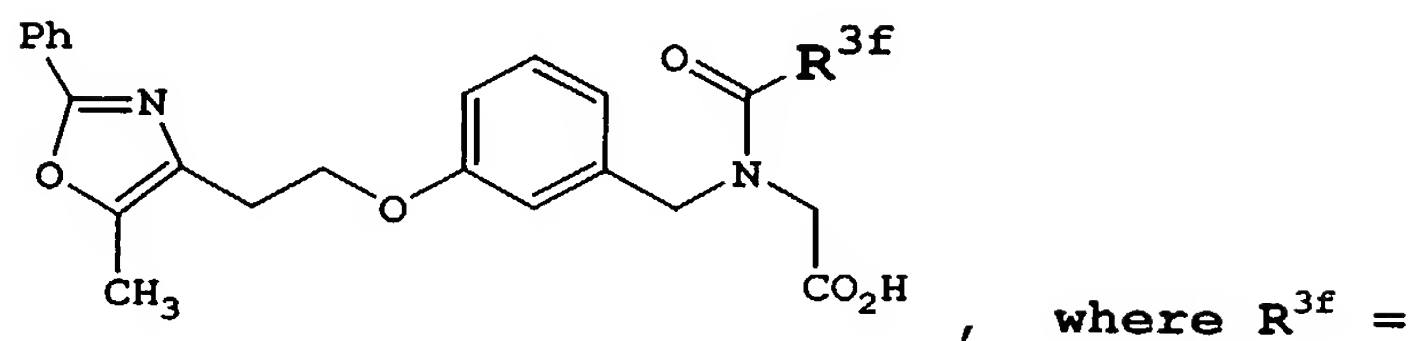
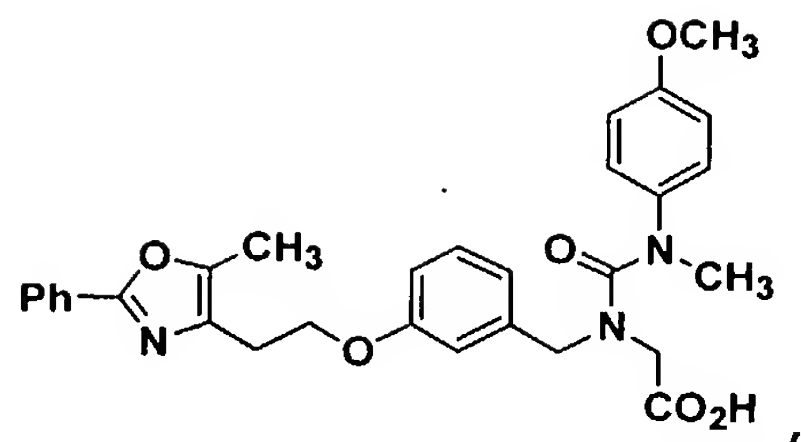


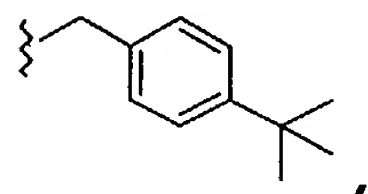
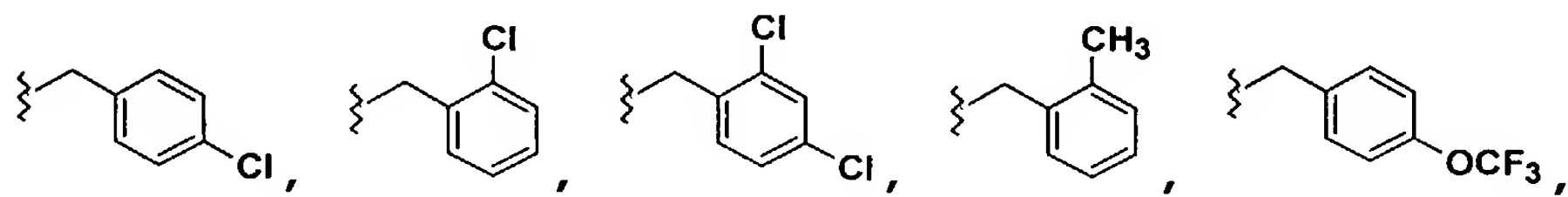
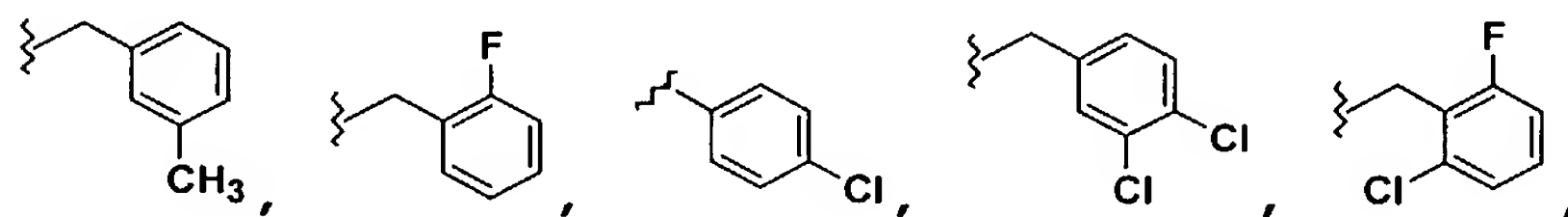
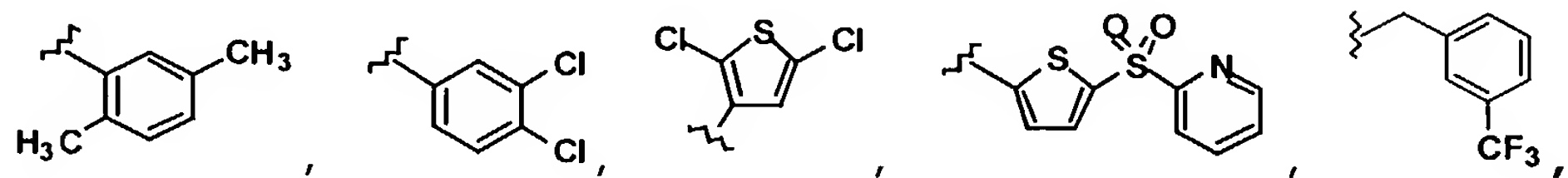
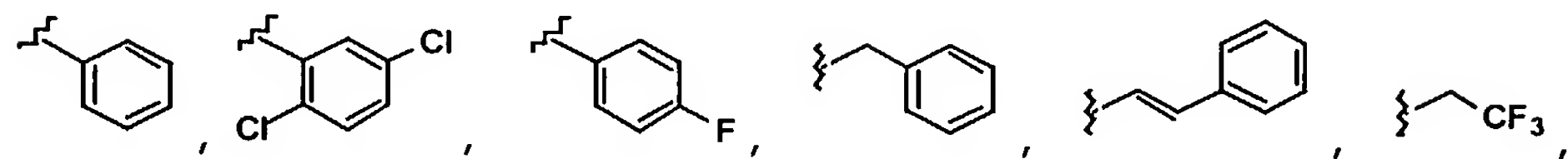
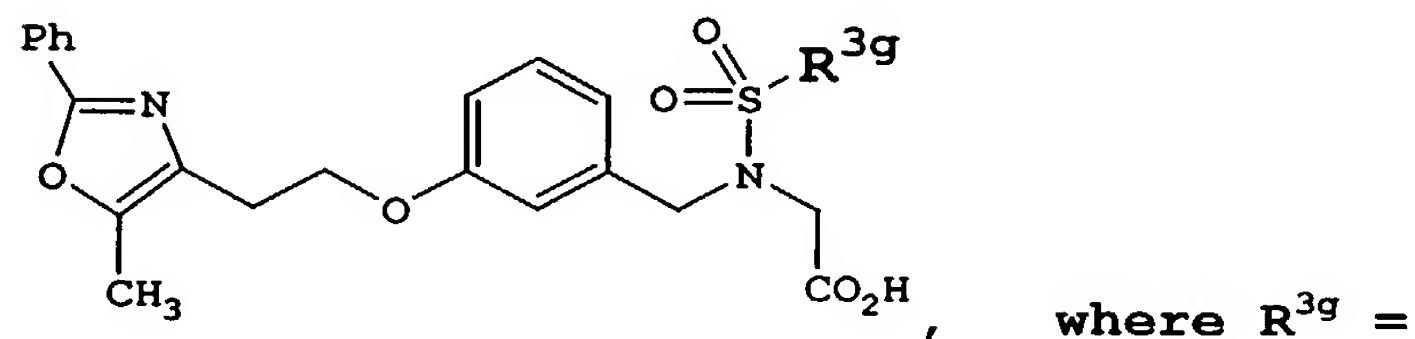
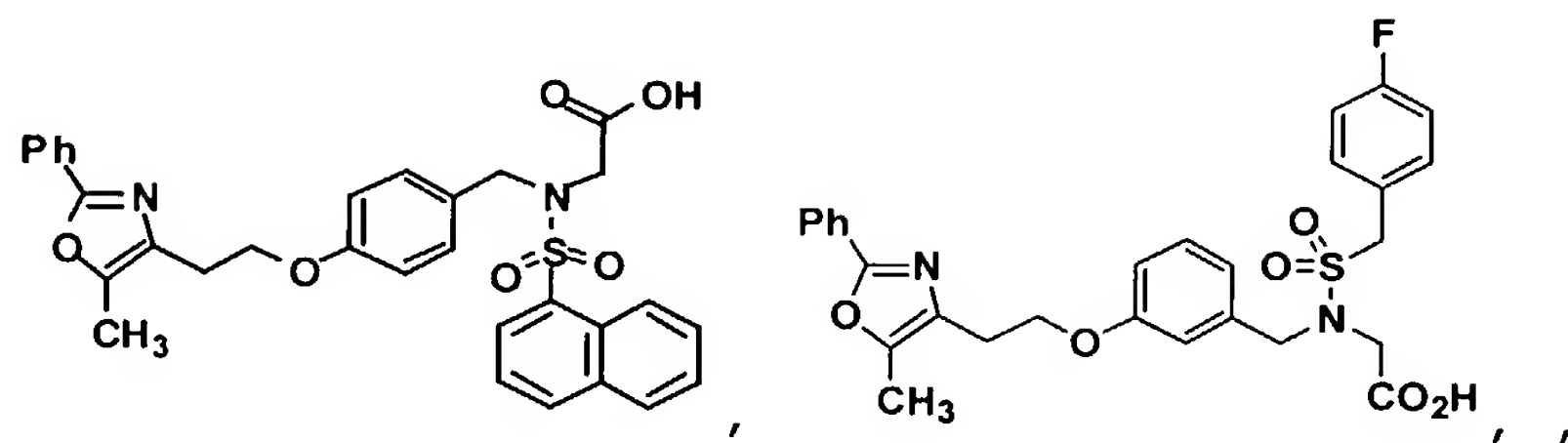


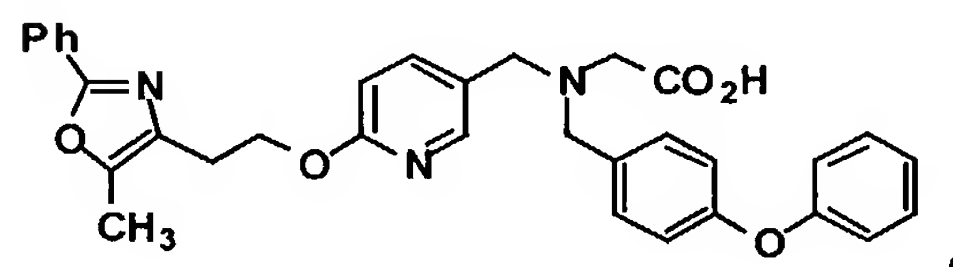
where  $R^{3e} =$

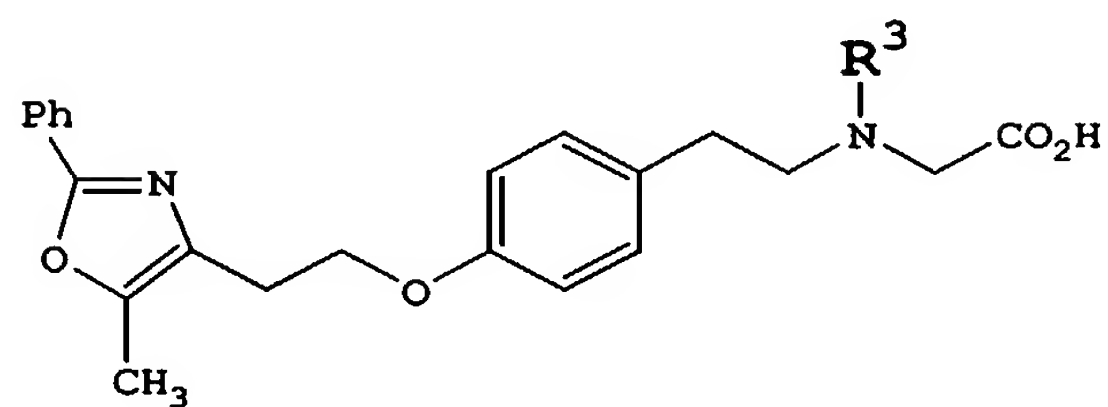




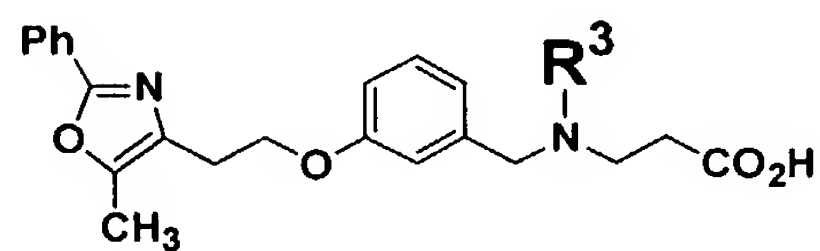
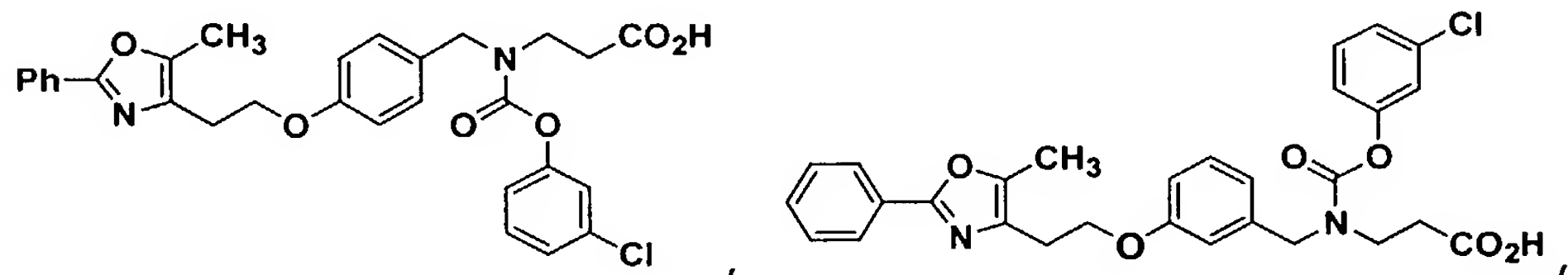
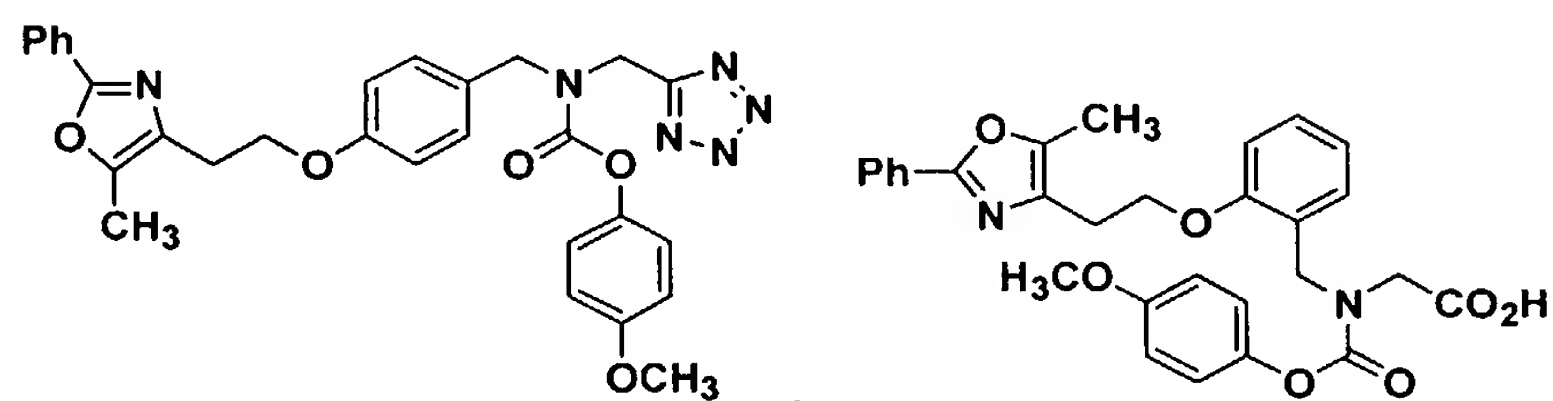
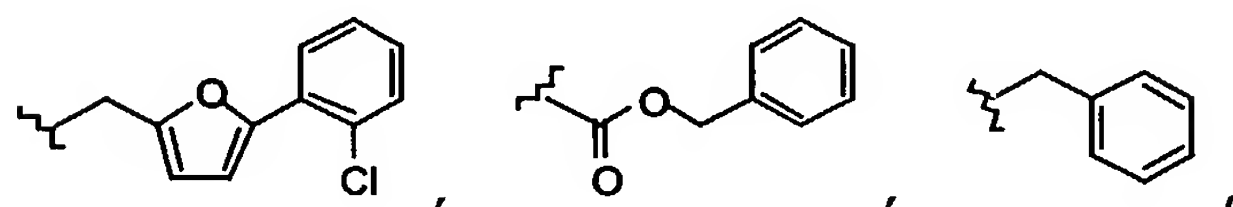




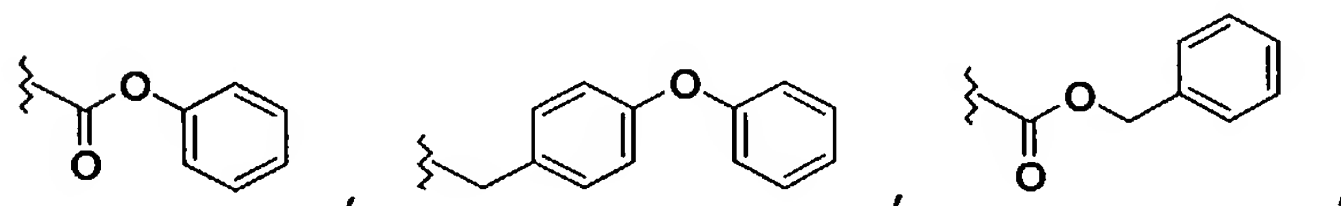




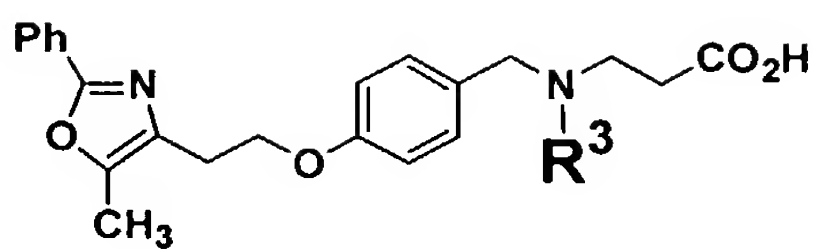
where  $R^3 =$



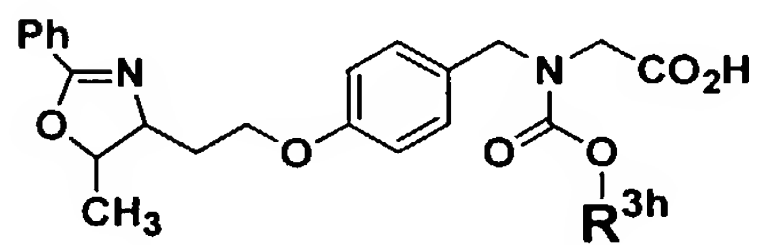
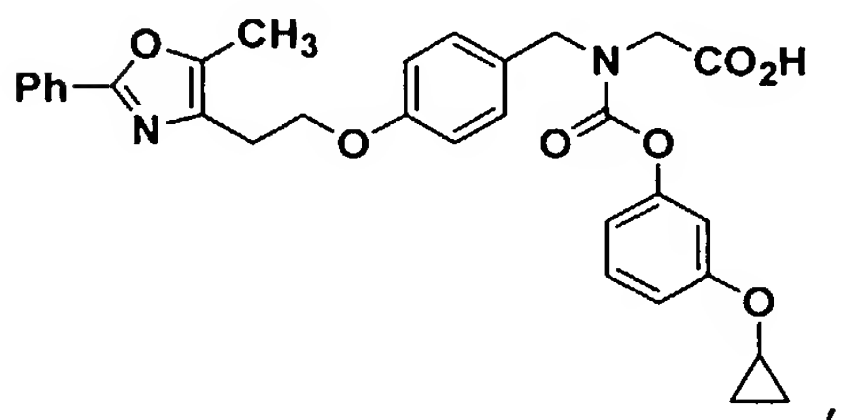
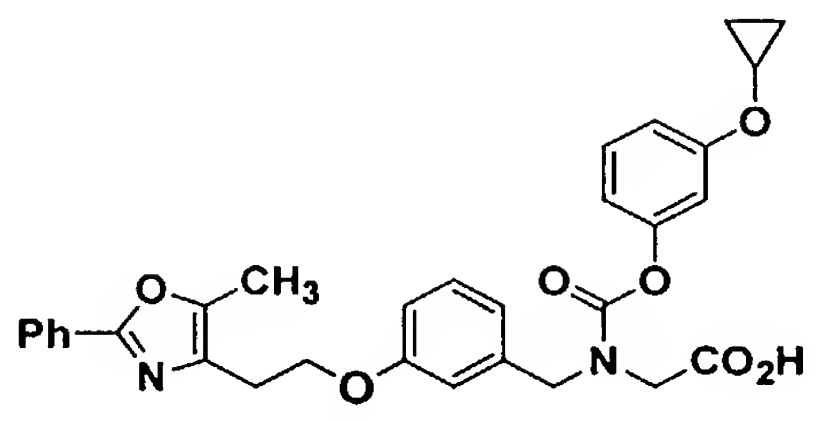
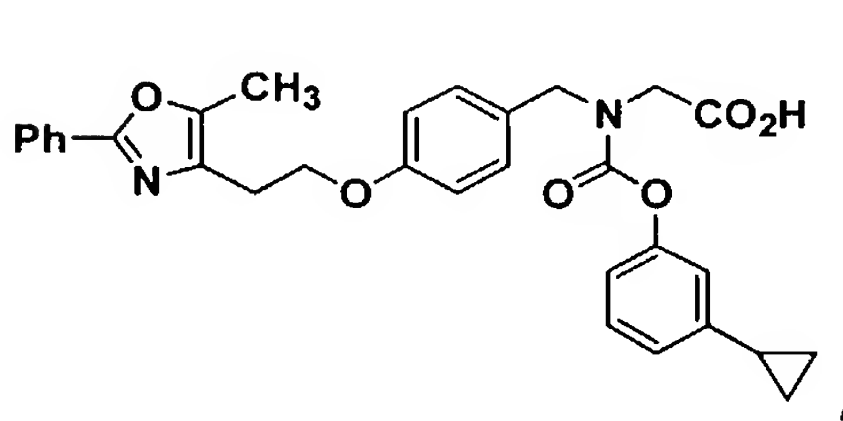
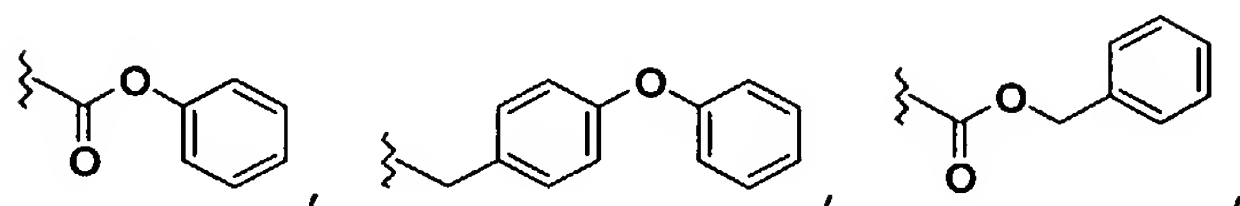
where  $R^3 =$



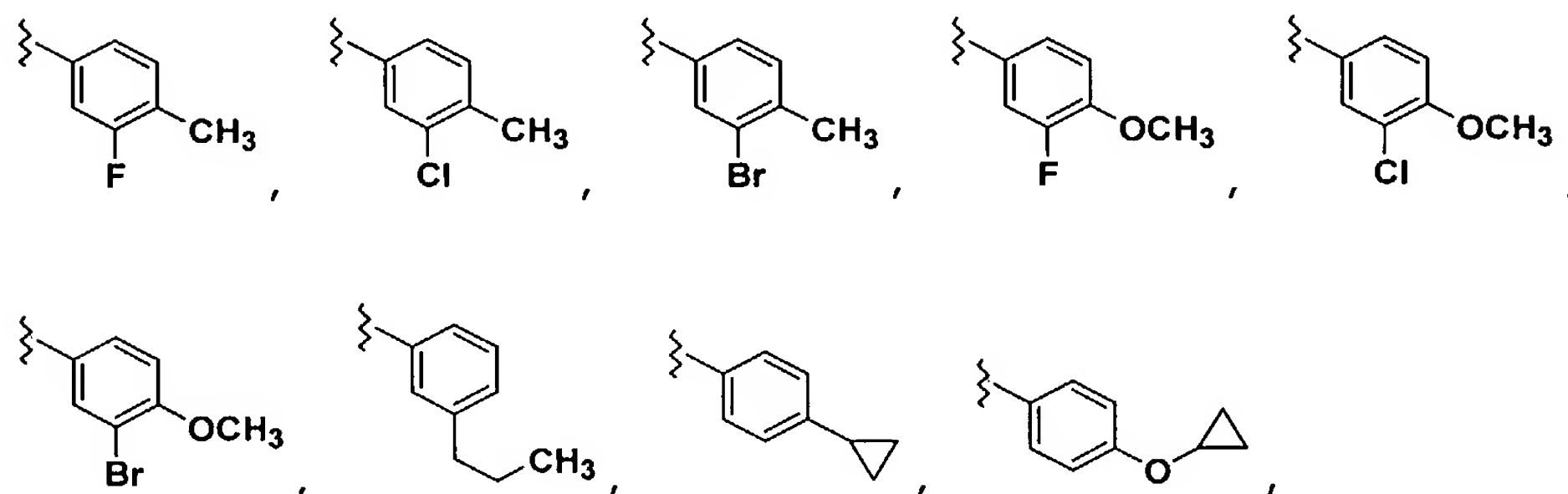


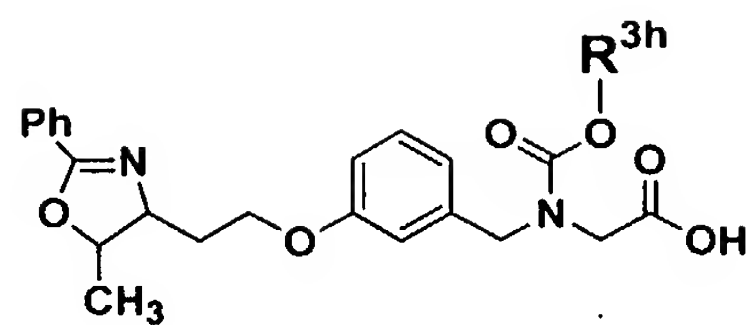


, where  $R^3 =$

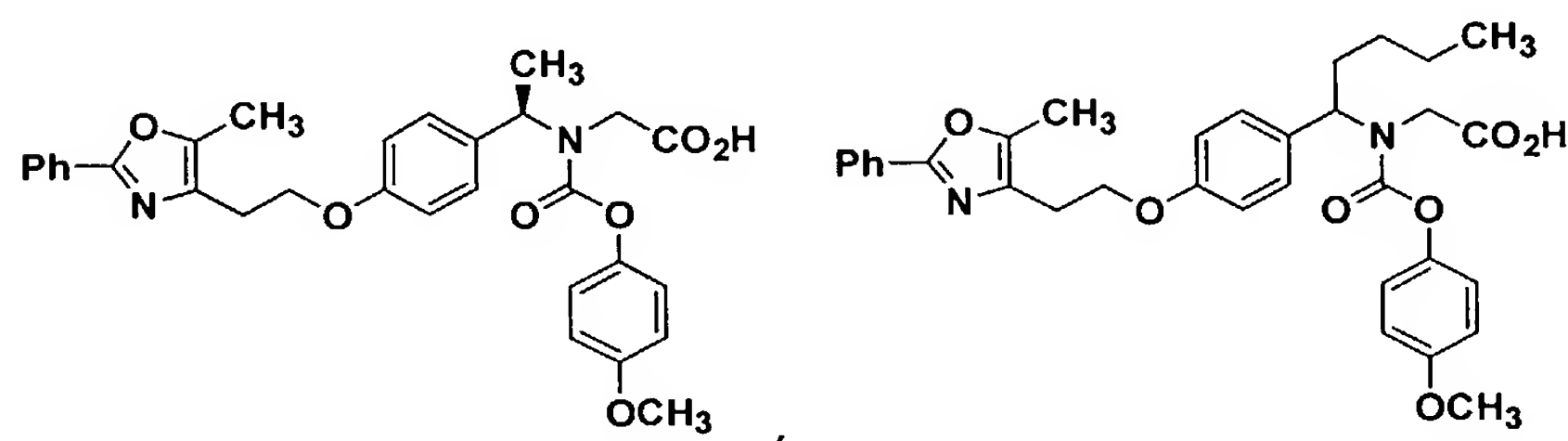
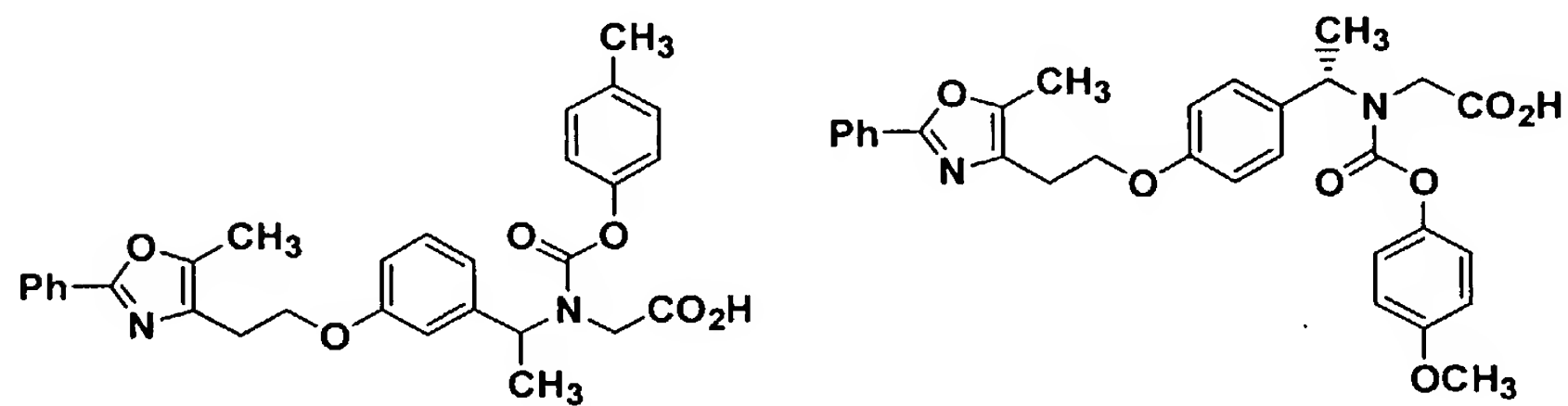
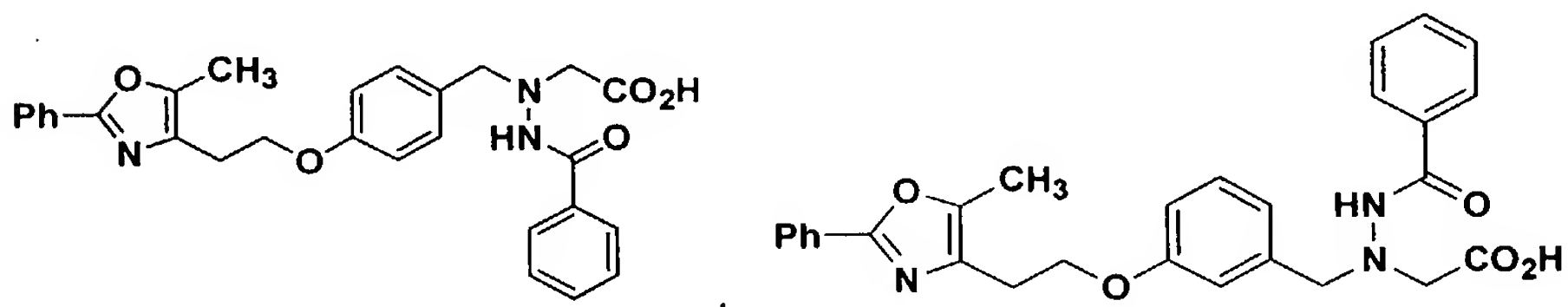
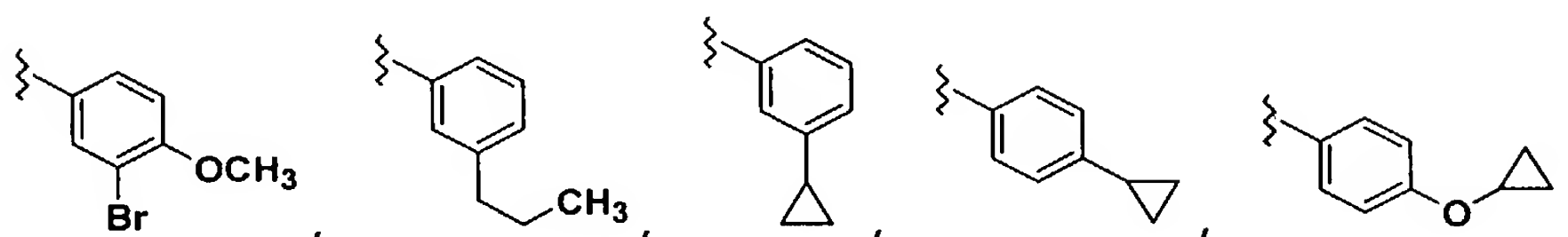
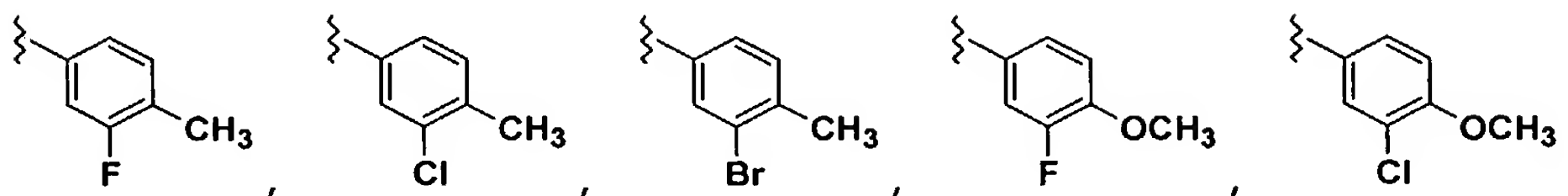


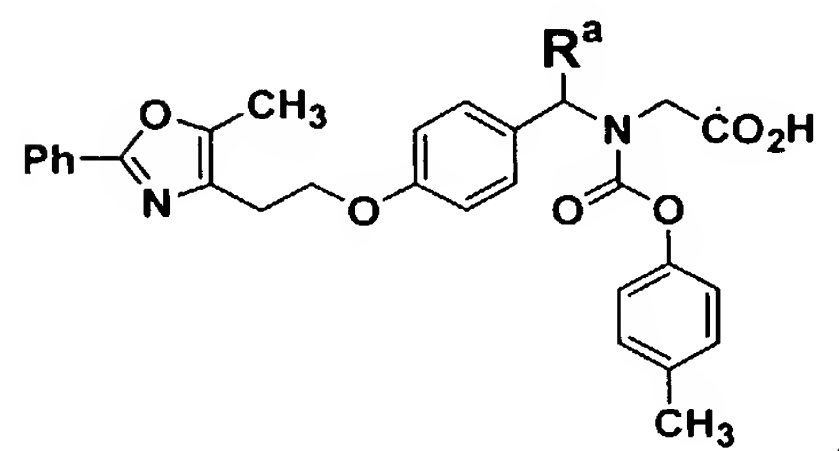
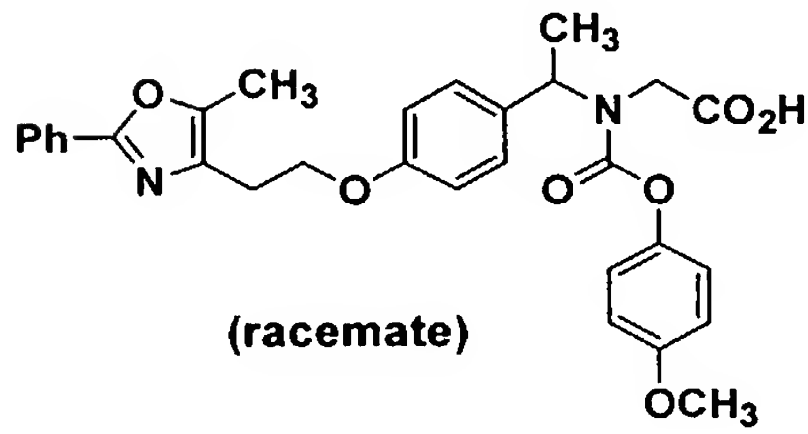
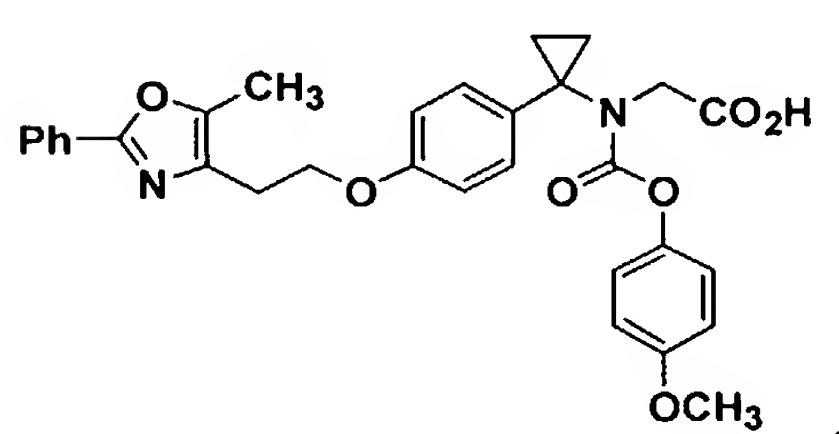
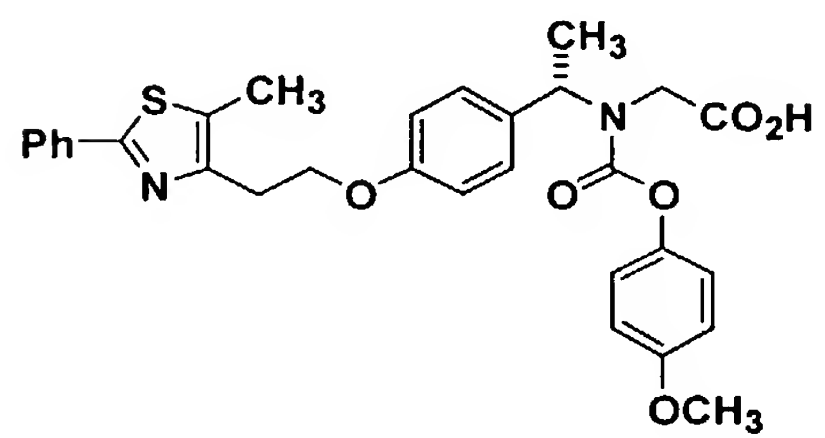
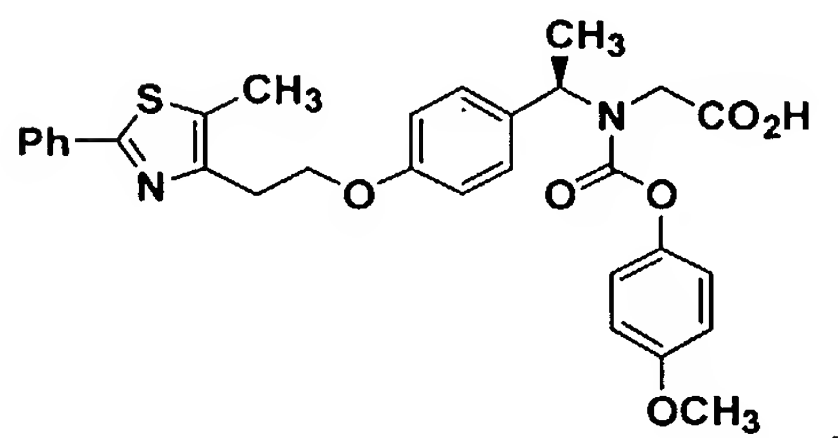
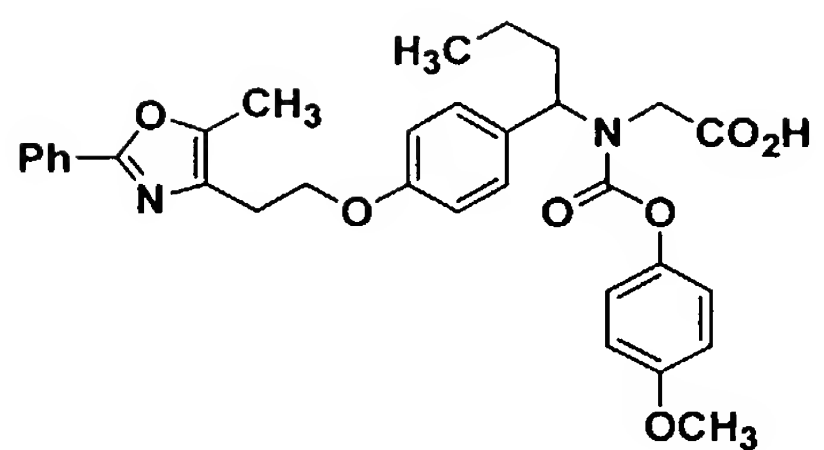
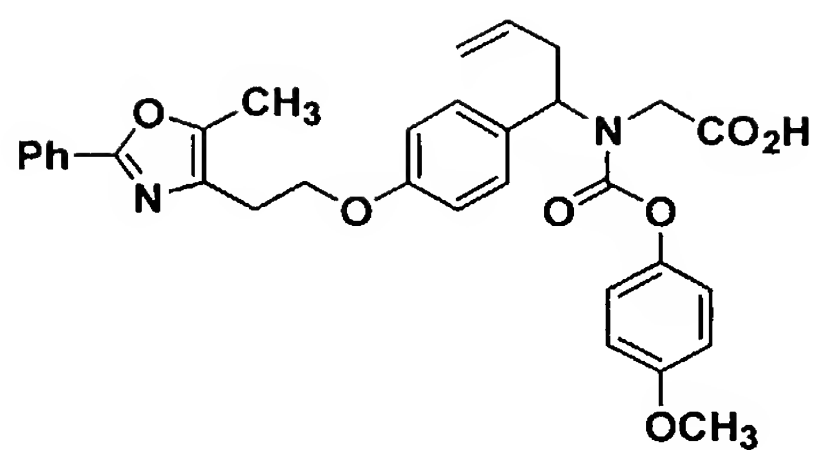
, where  $R^{3h} =$



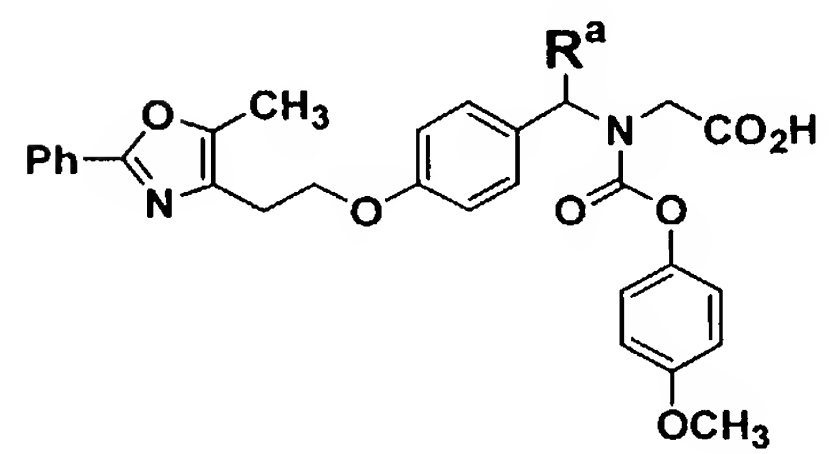


, where  $R^{3h} =$

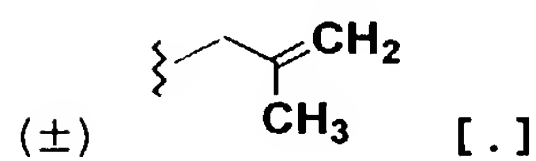


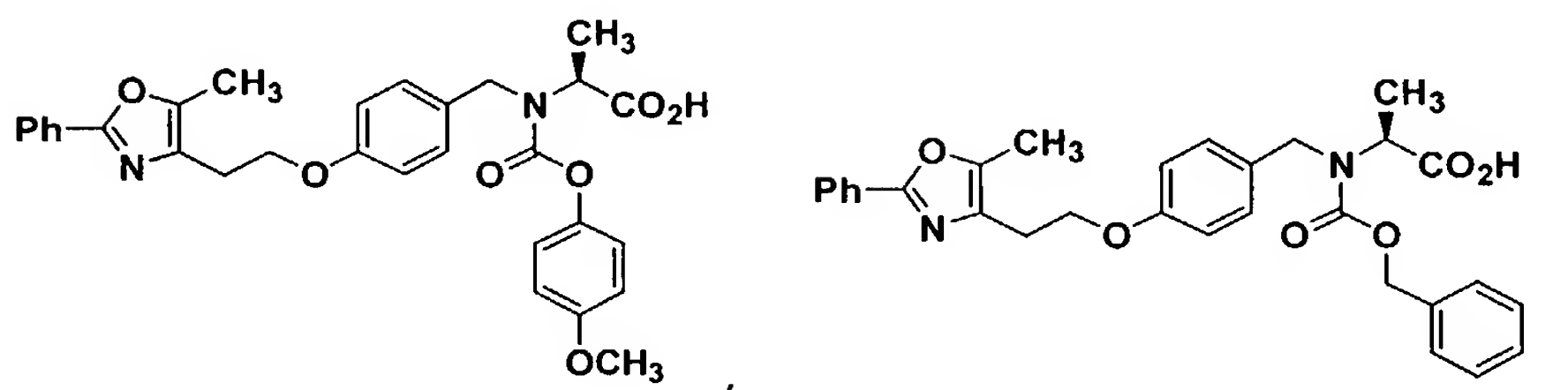
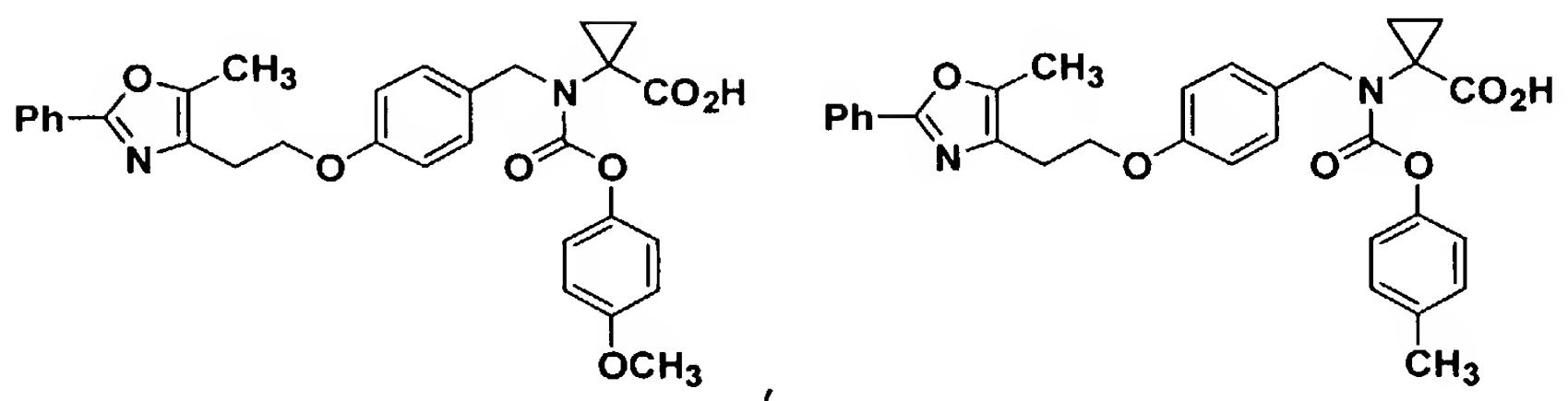
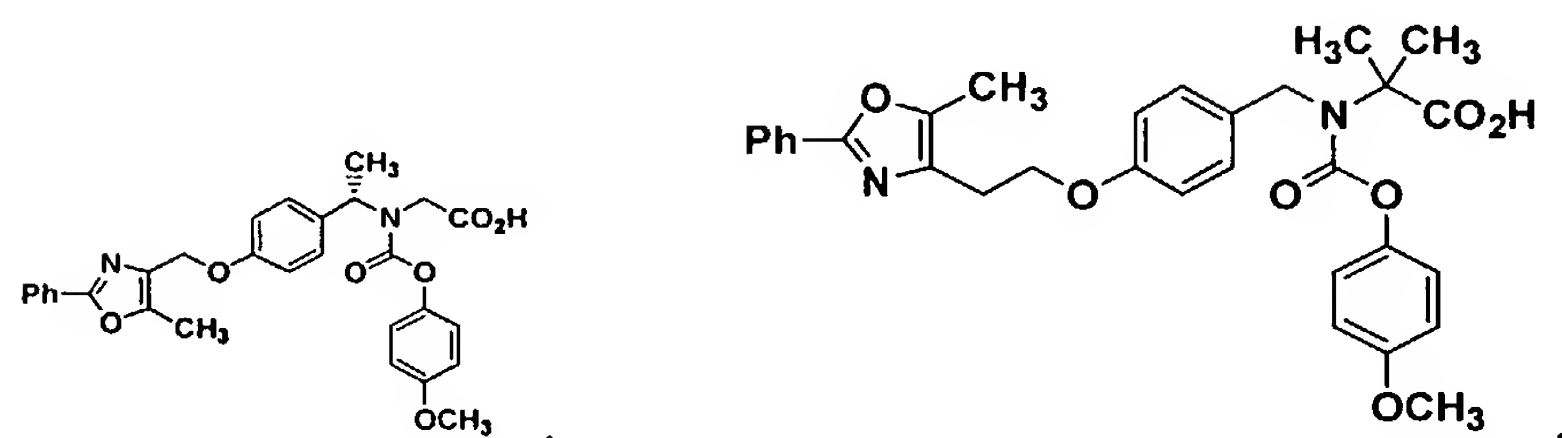
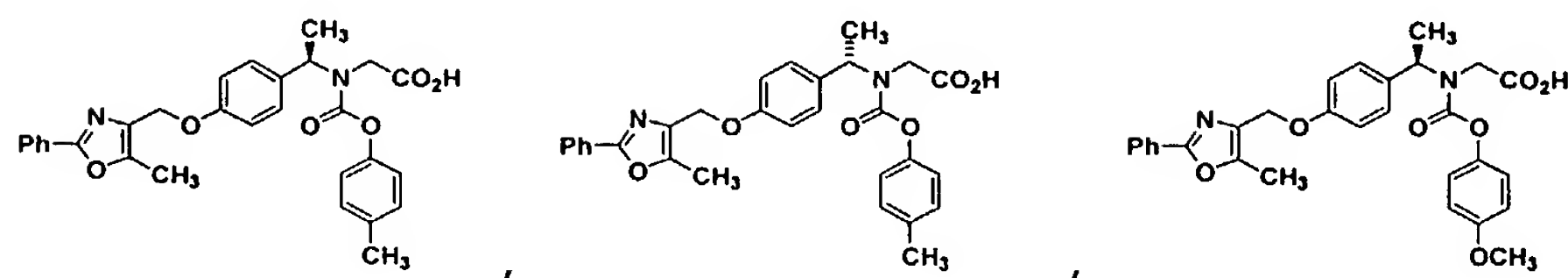
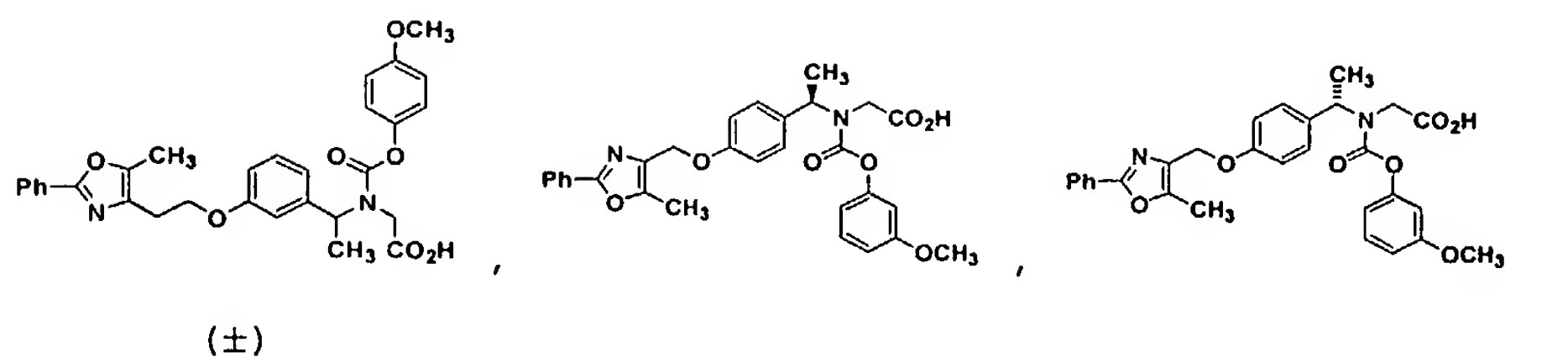


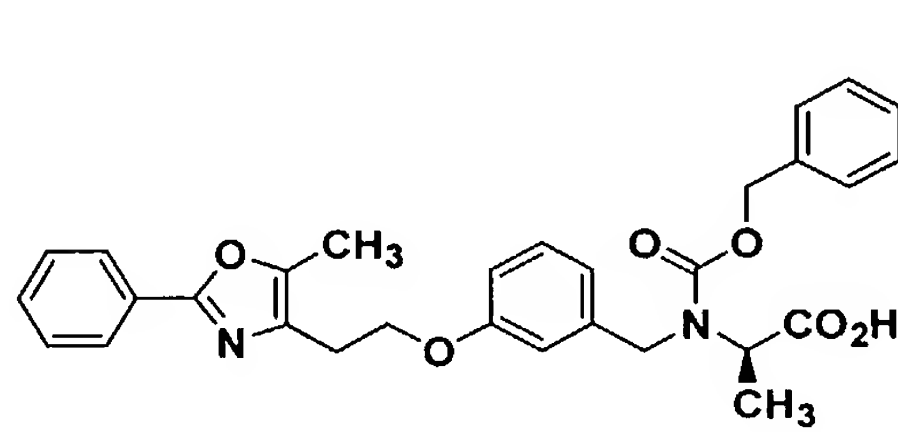
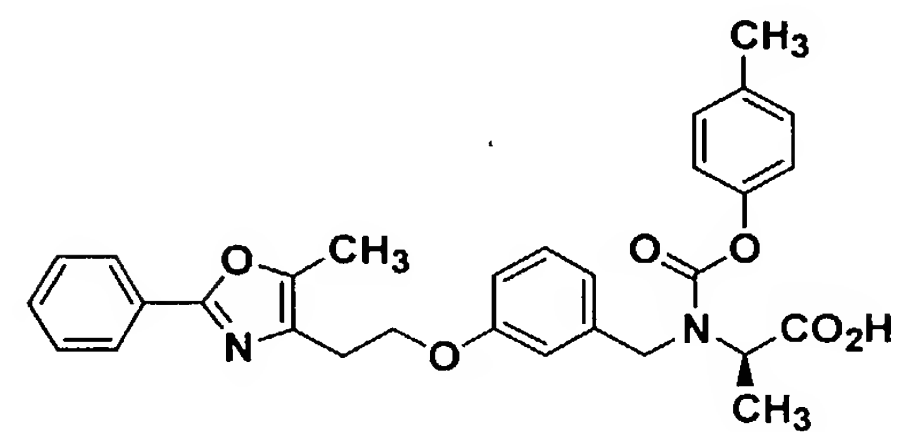
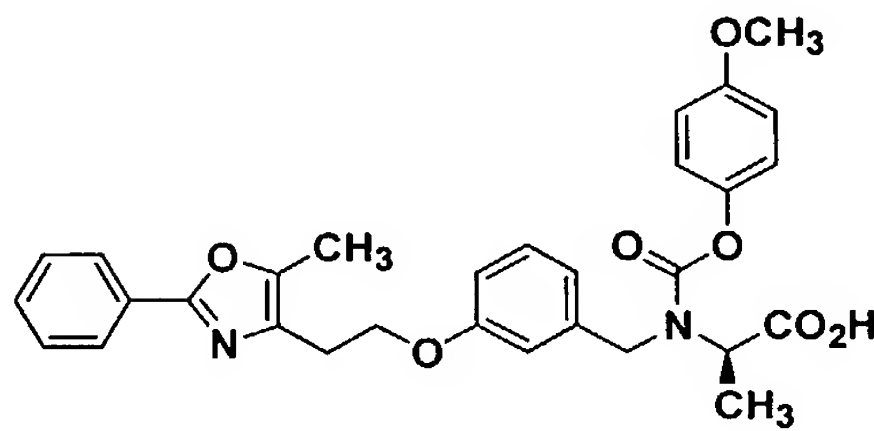
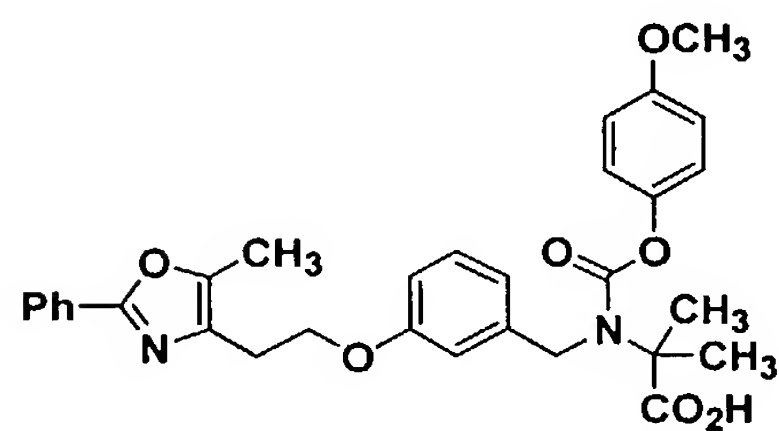
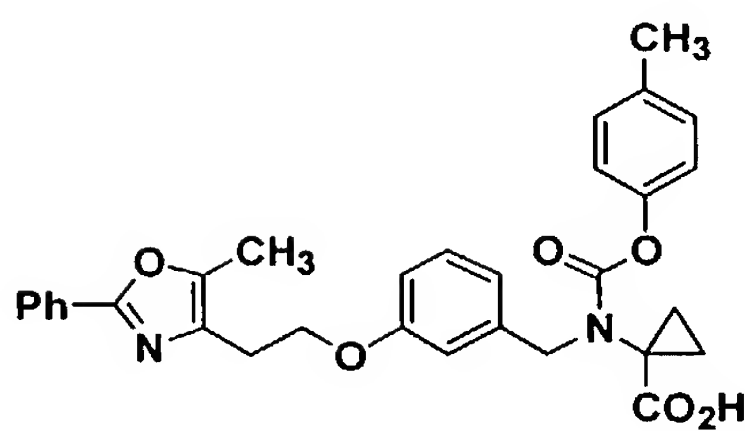
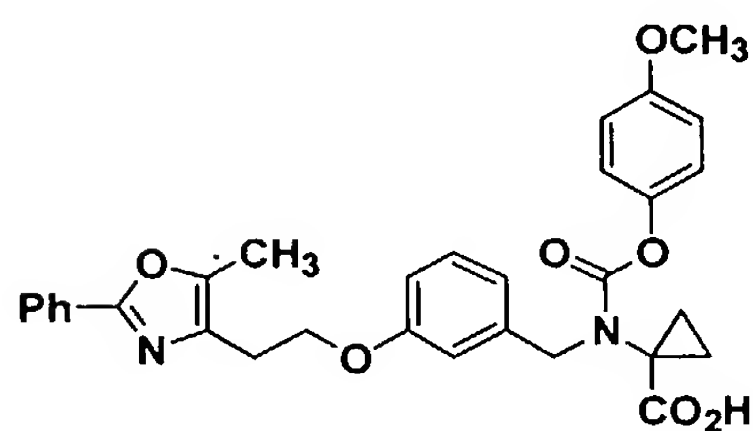
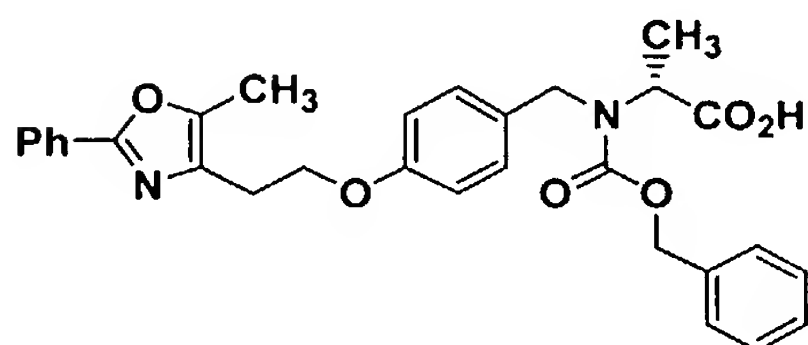
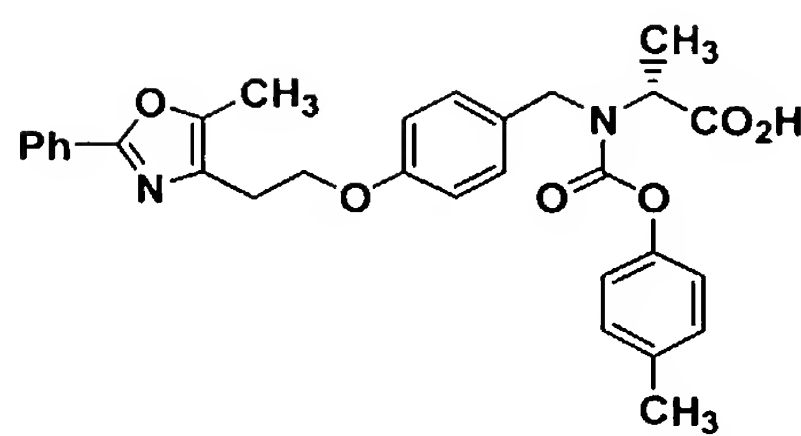
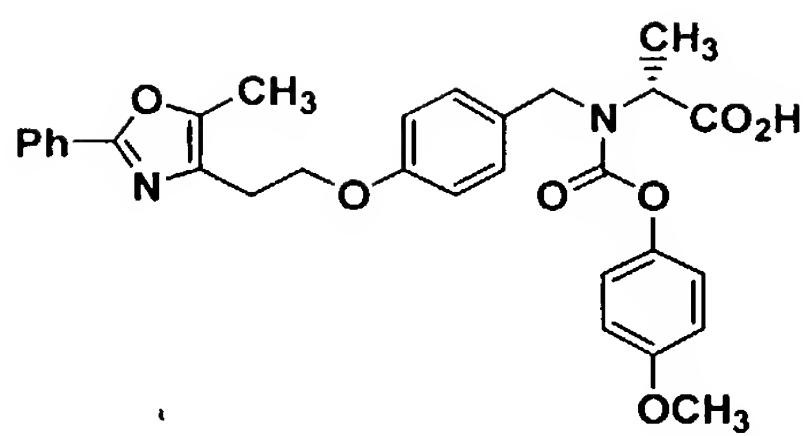
where  $R^a = (\pm)\text{-Me}$  ,  $(\pm)\text{ n-Bu}$  ,

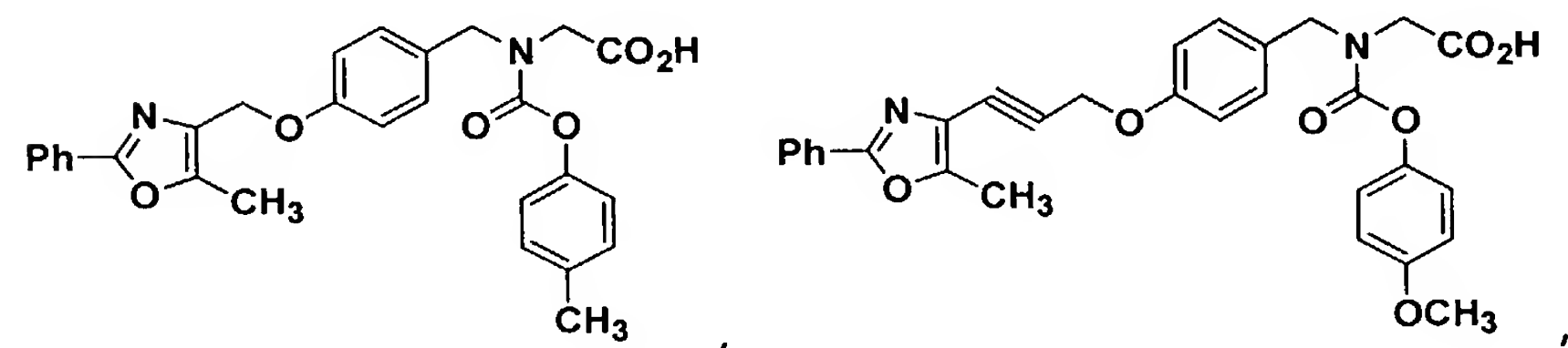
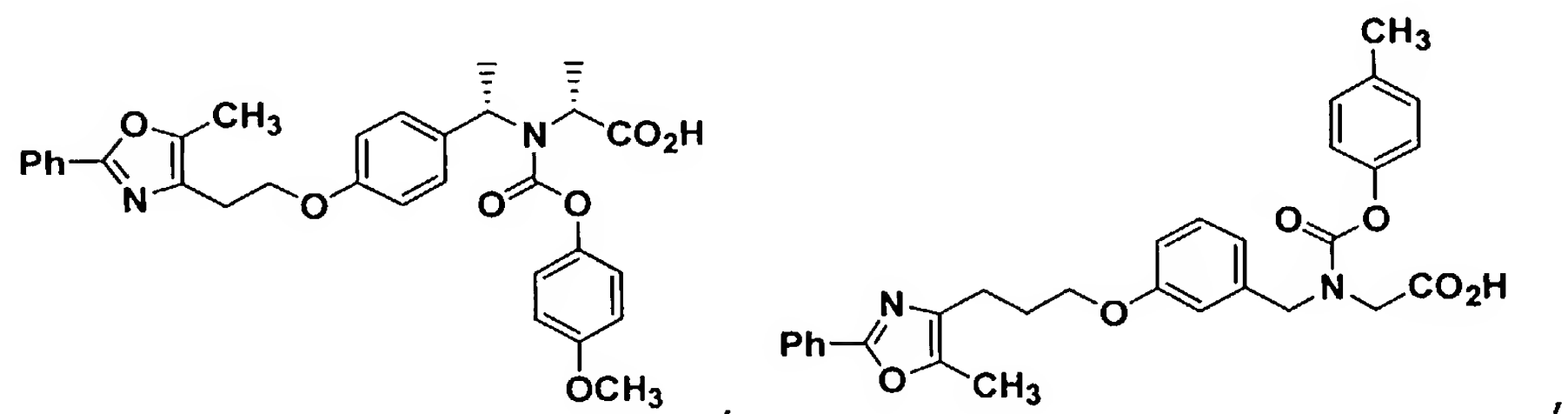
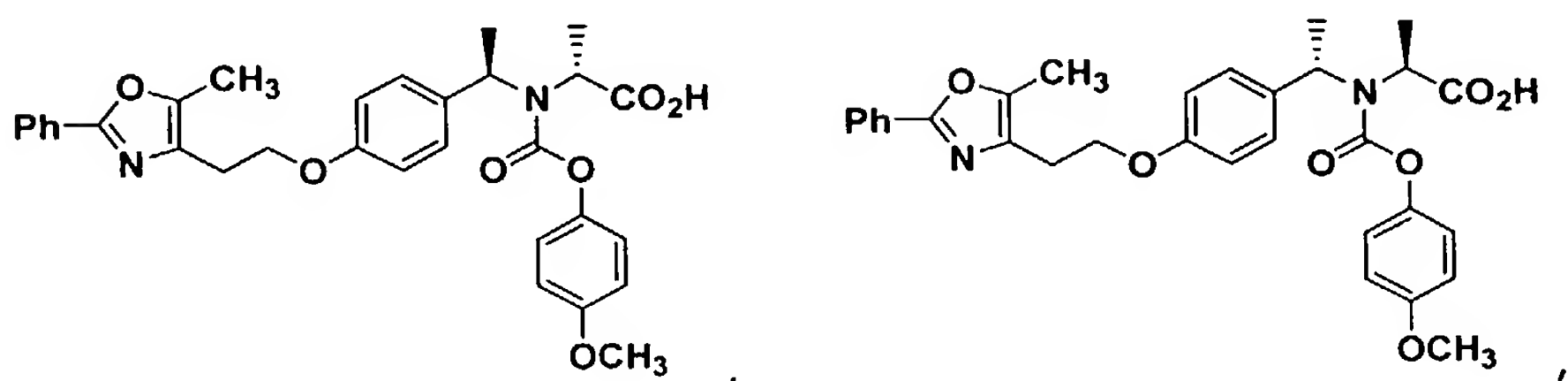
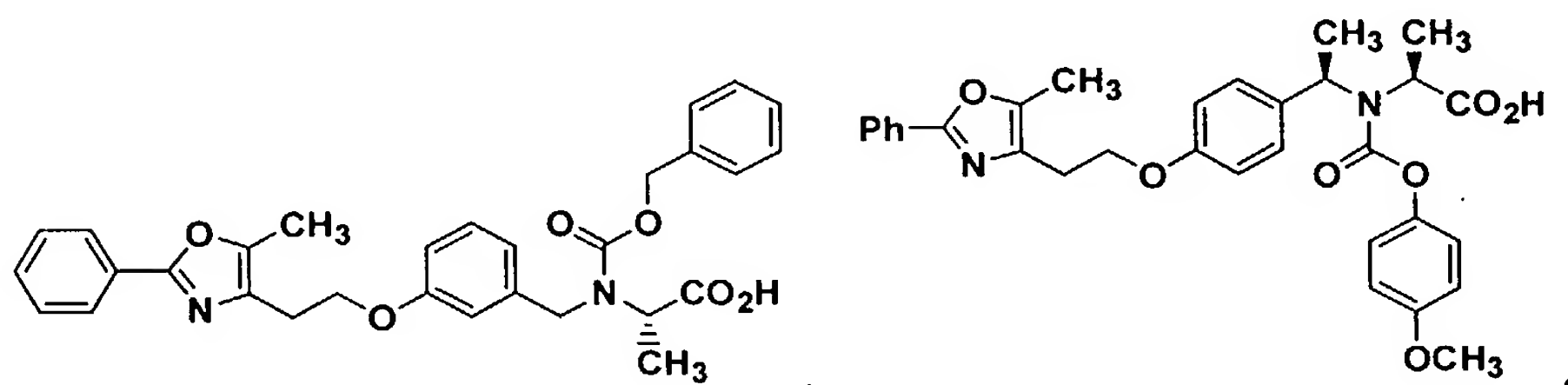
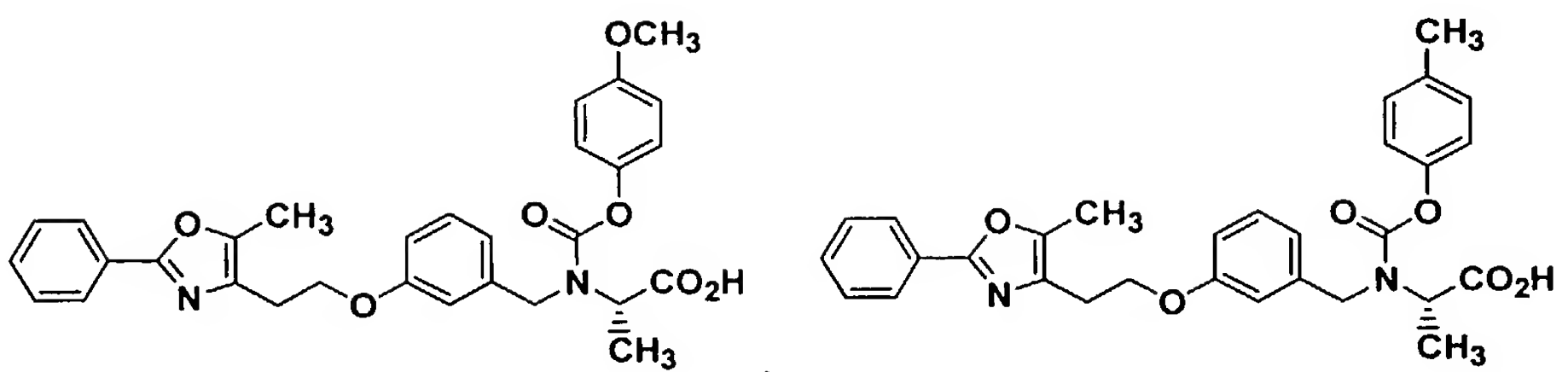


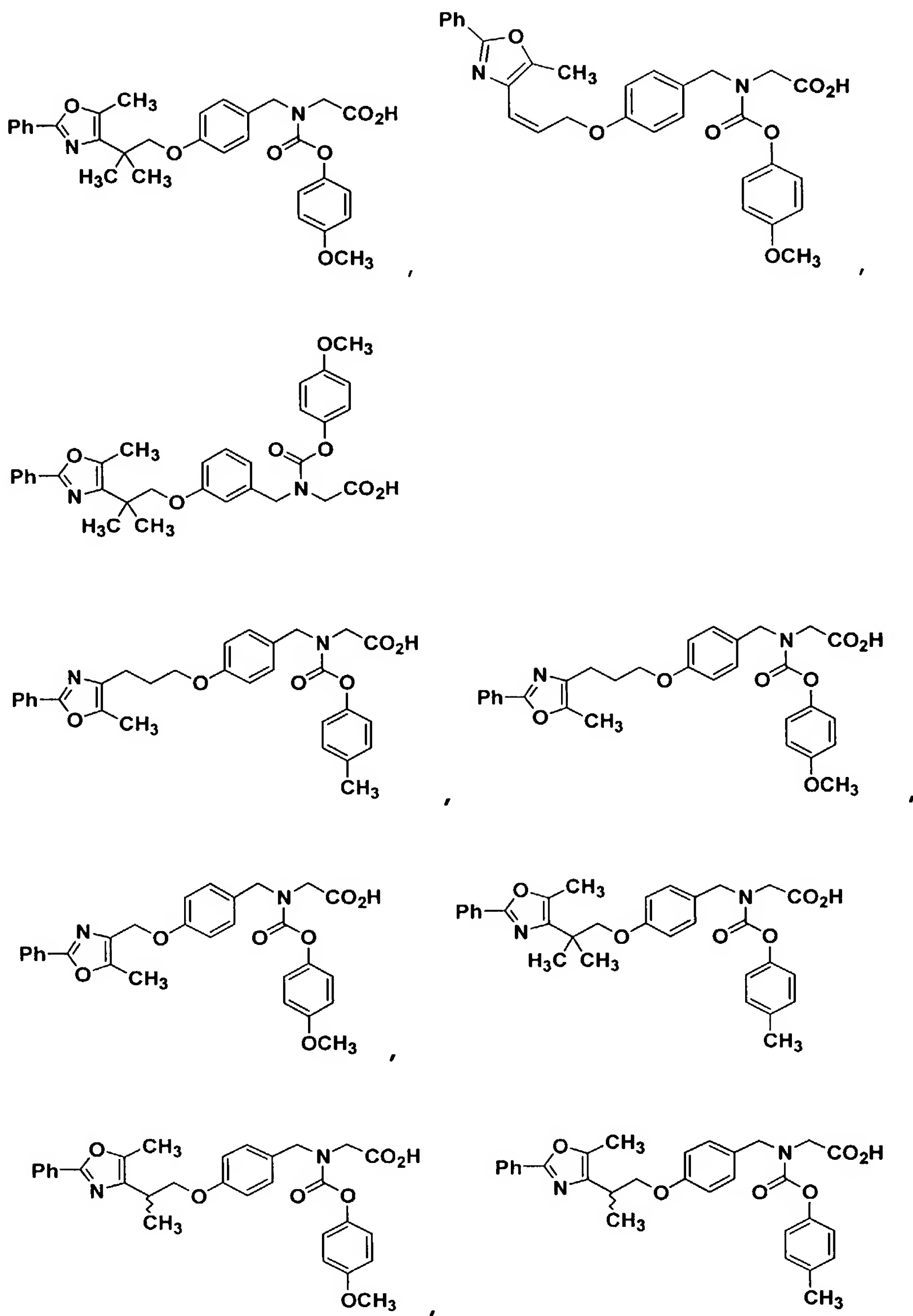
where  $R^a = (\pm)\text{ Et}$  ,  $(\pm)\text{ i-Bu}$  ,

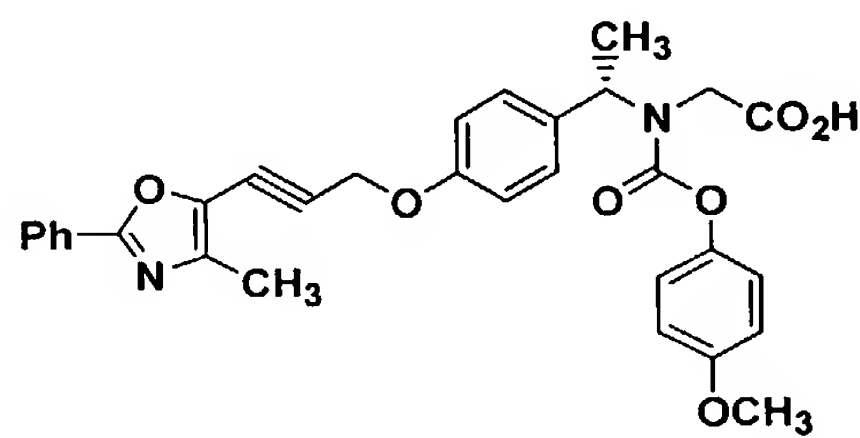
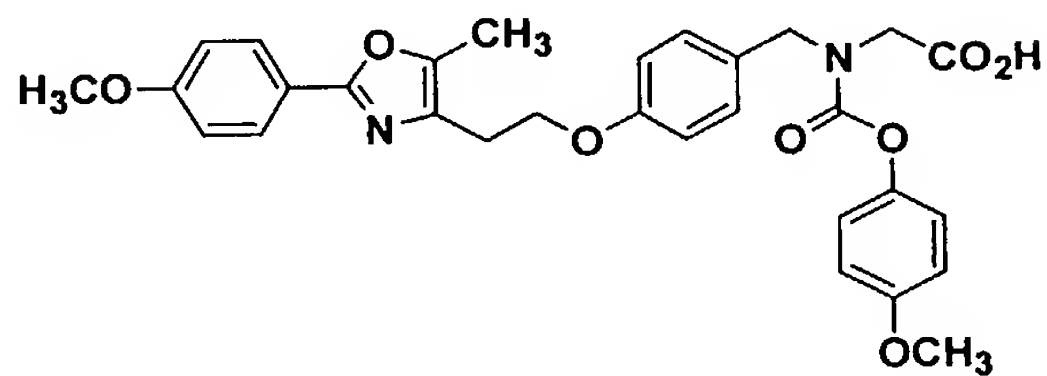
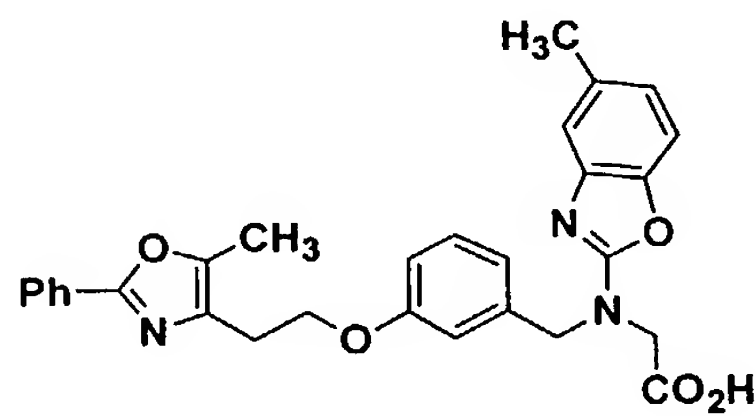
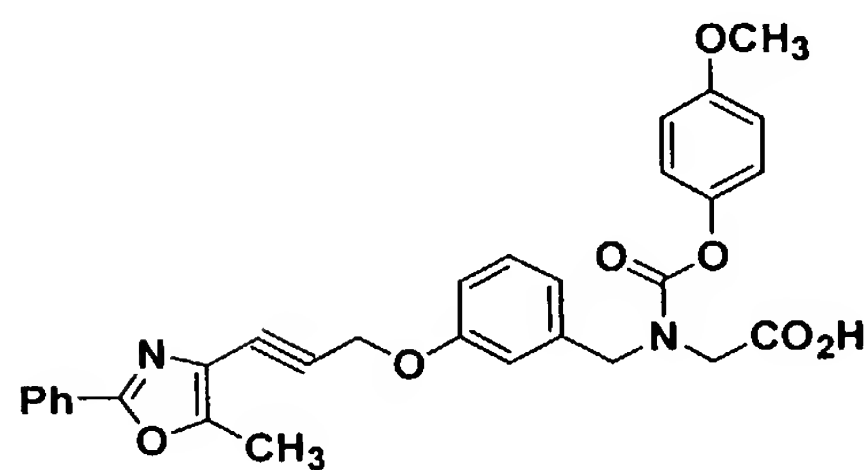
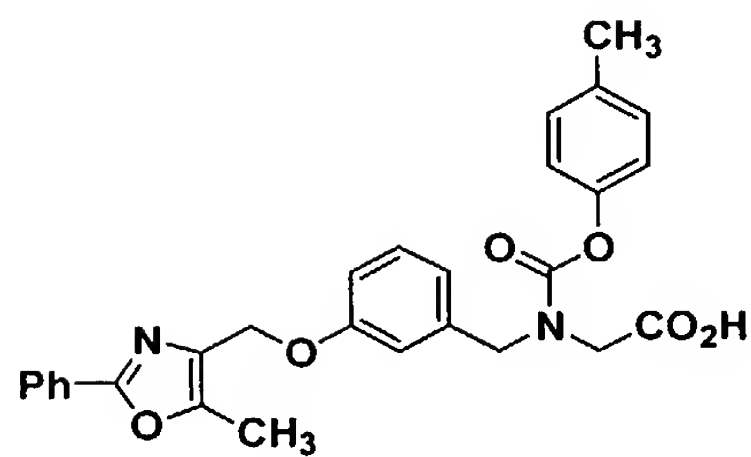




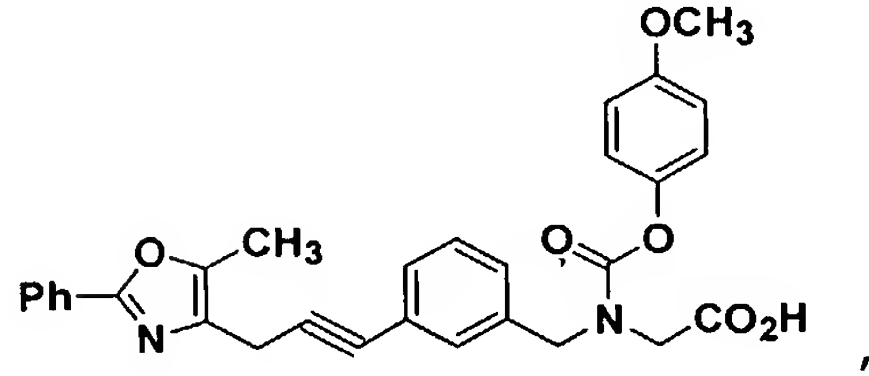
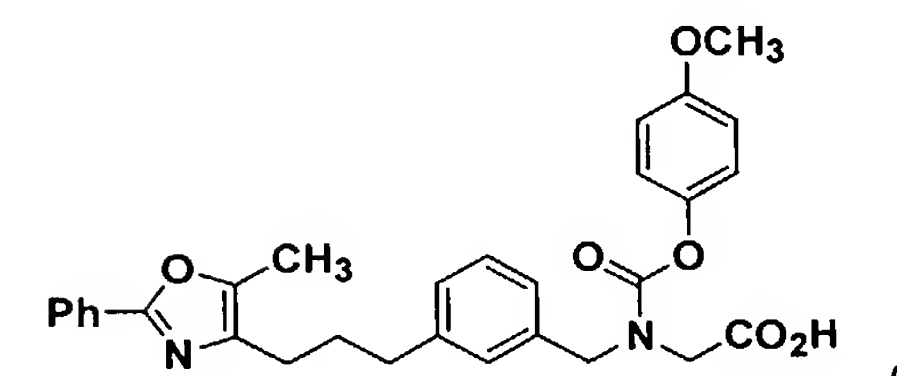
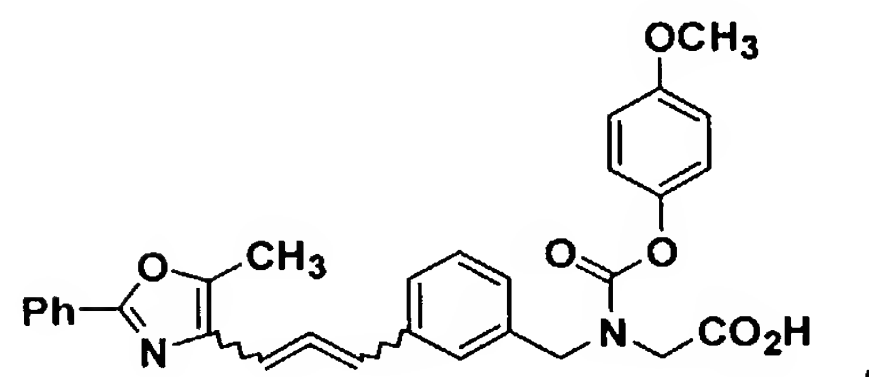
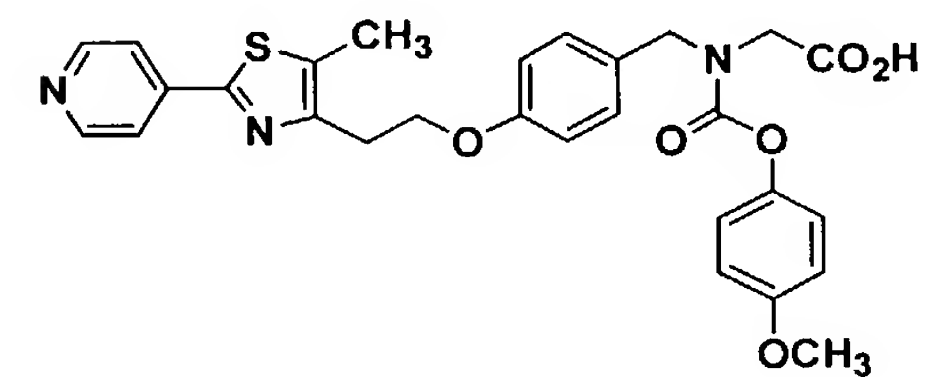
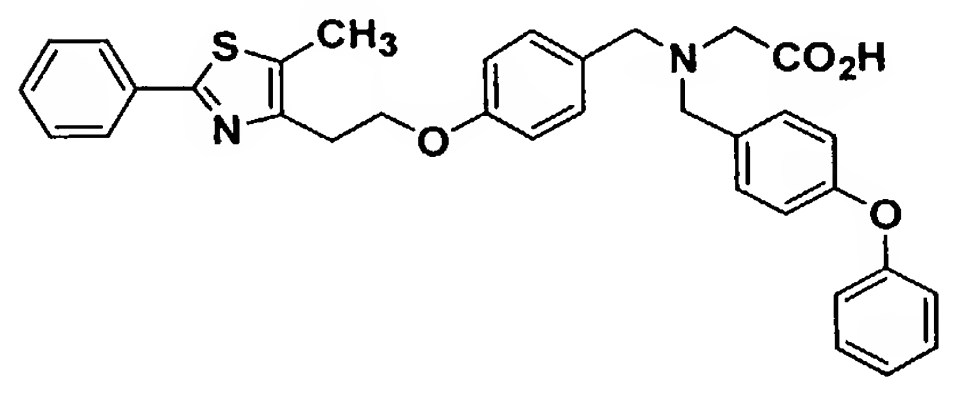
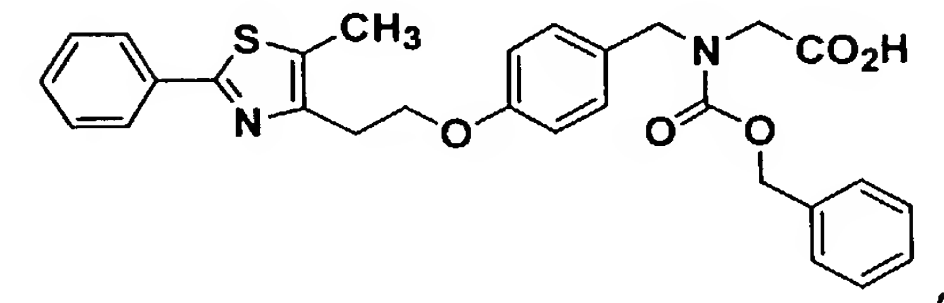
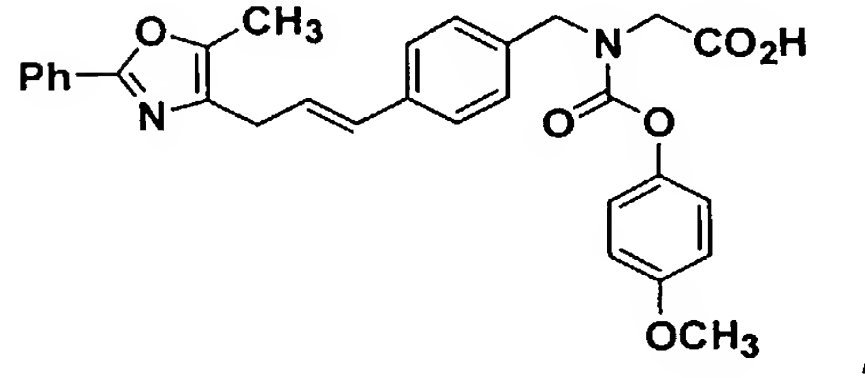
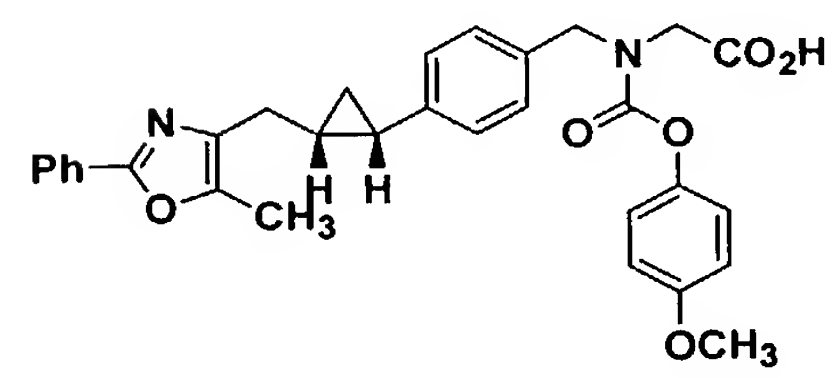
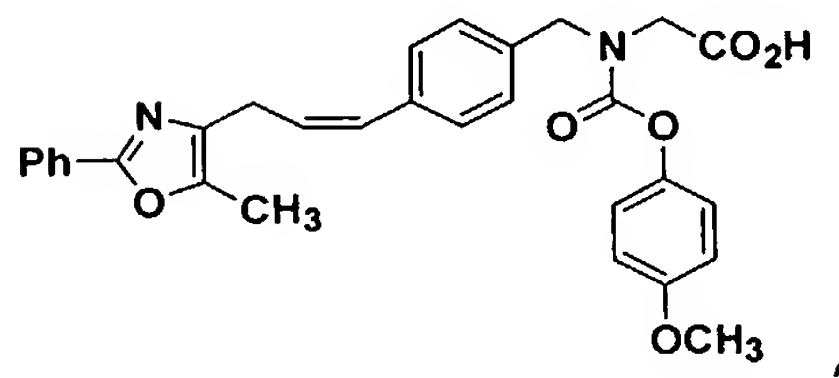
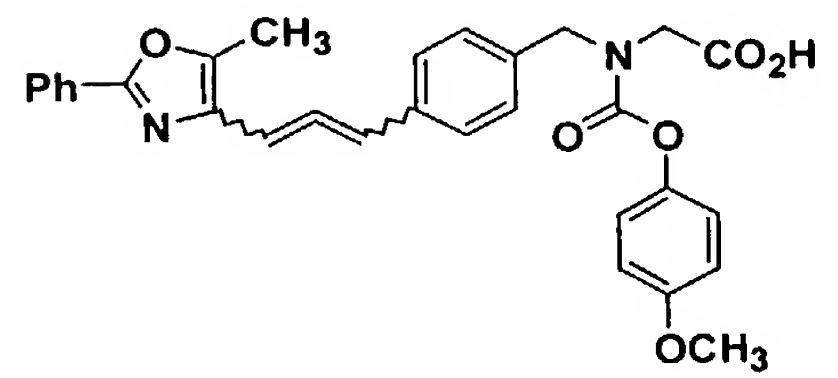
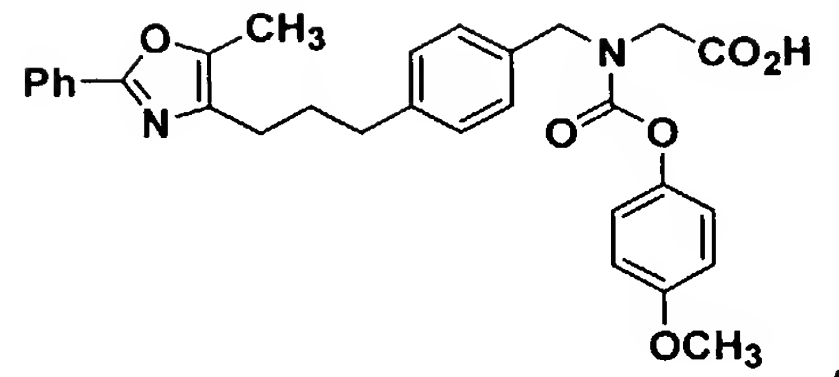
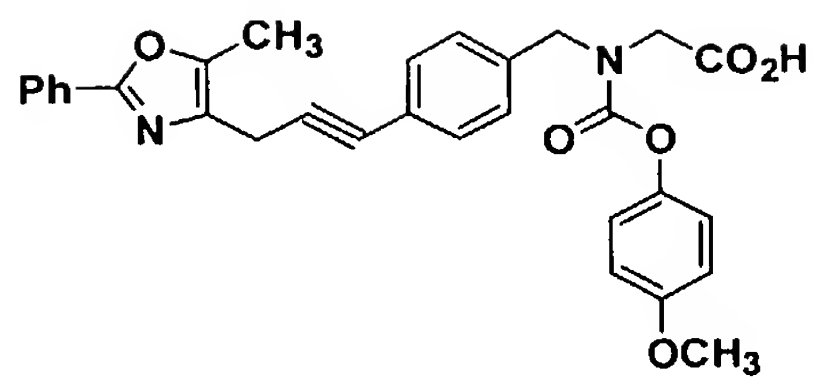


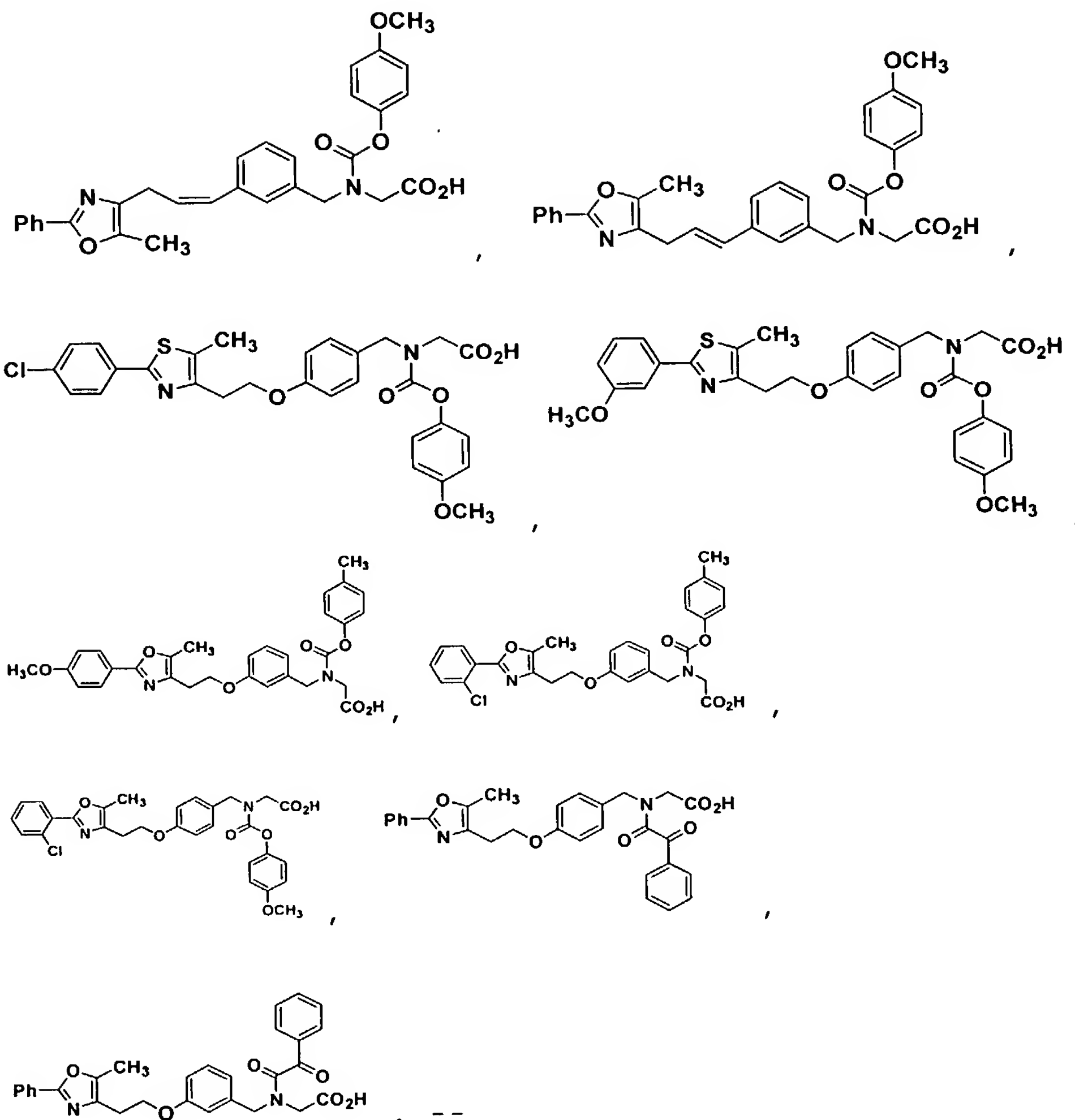




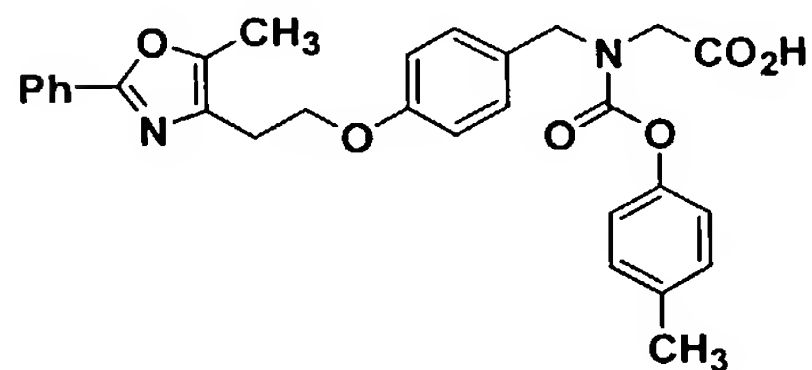
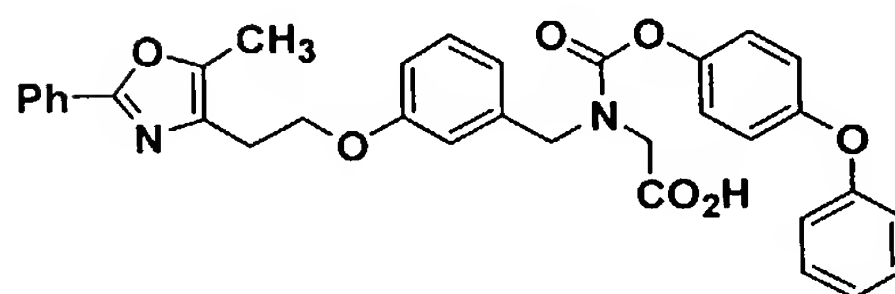
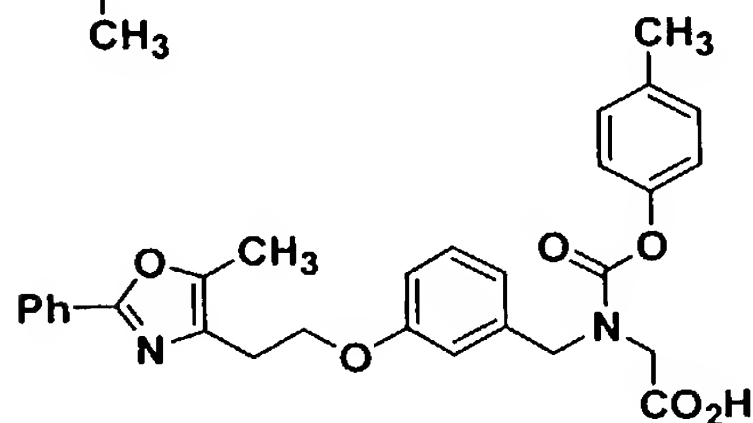
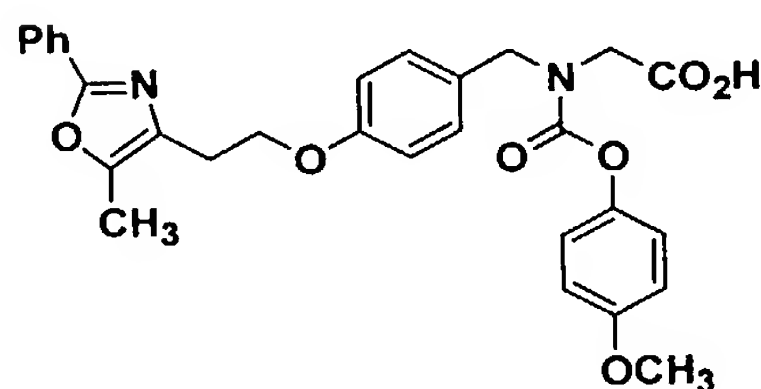
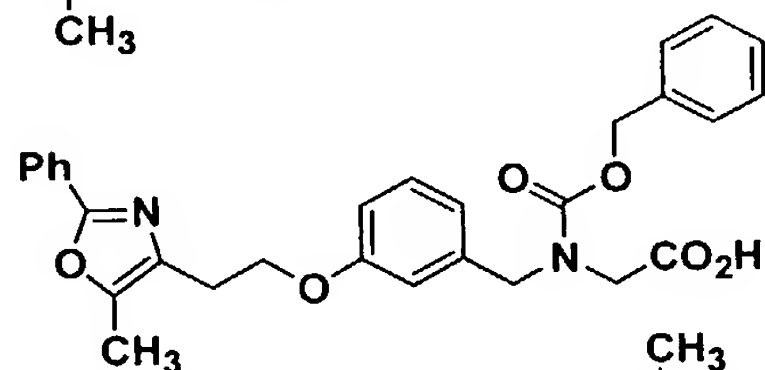
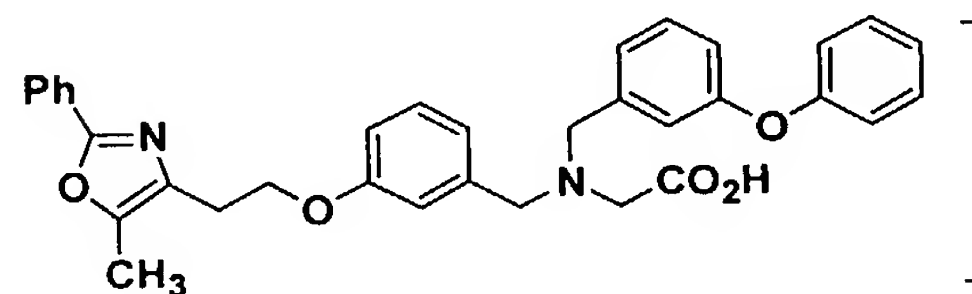
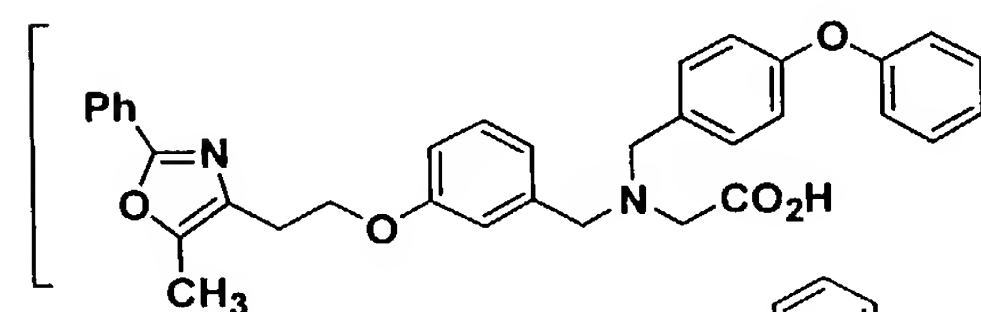
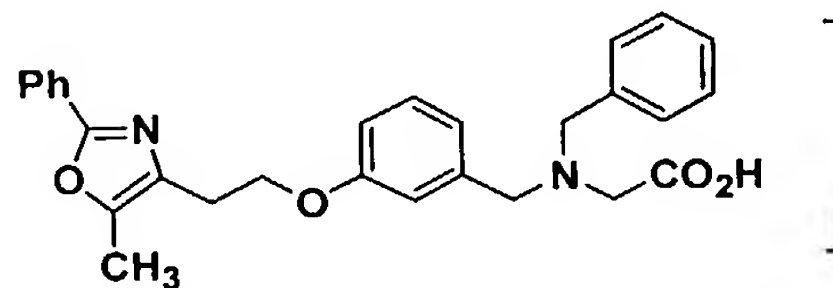
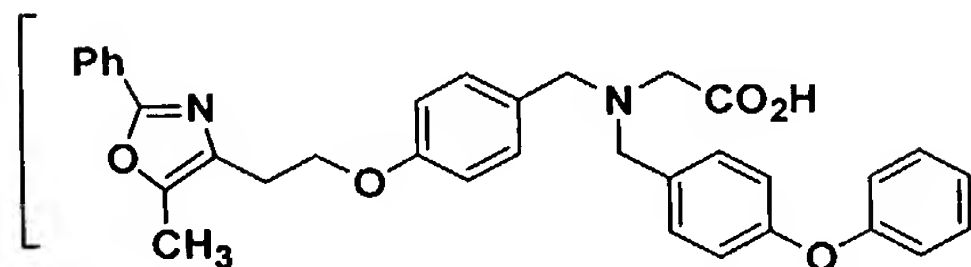
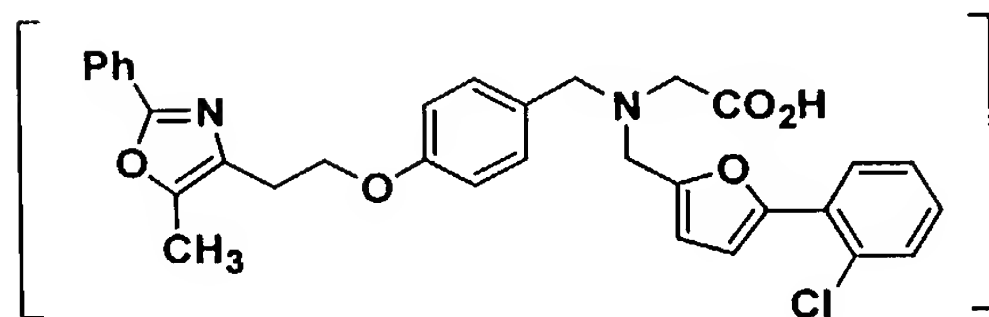
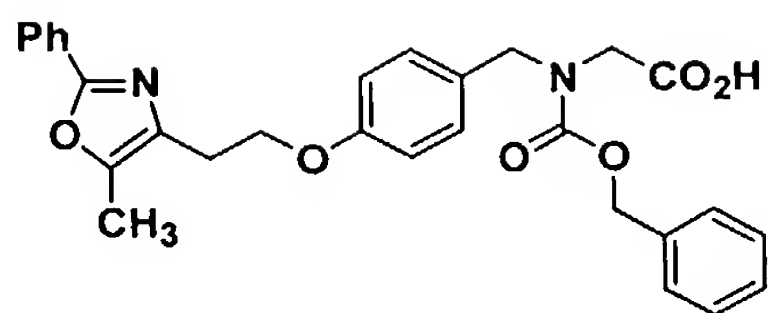


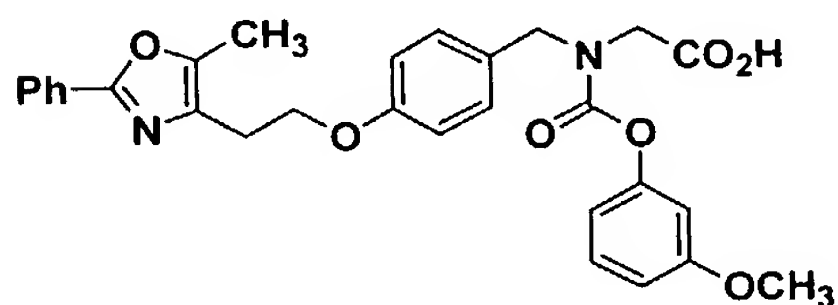


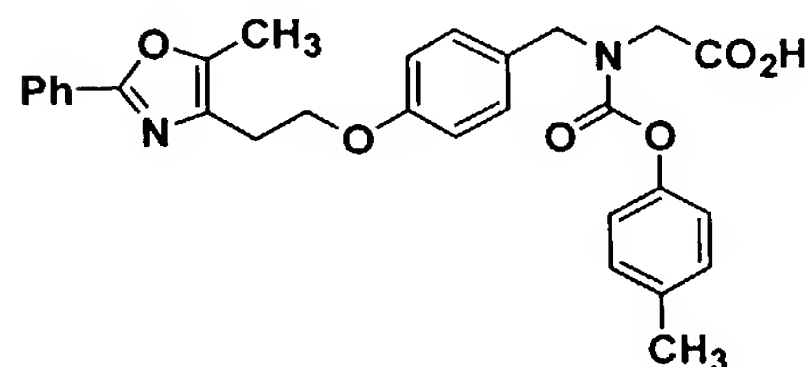
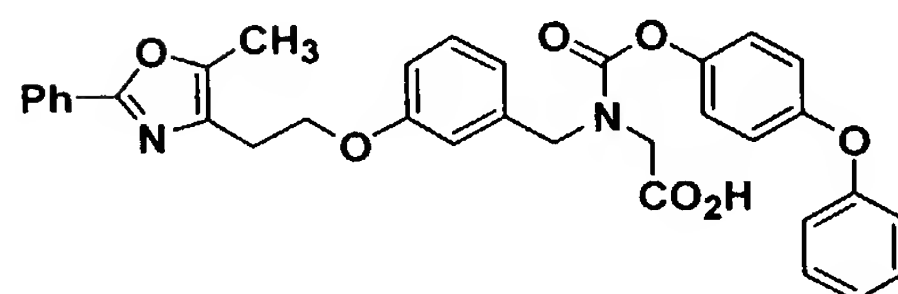
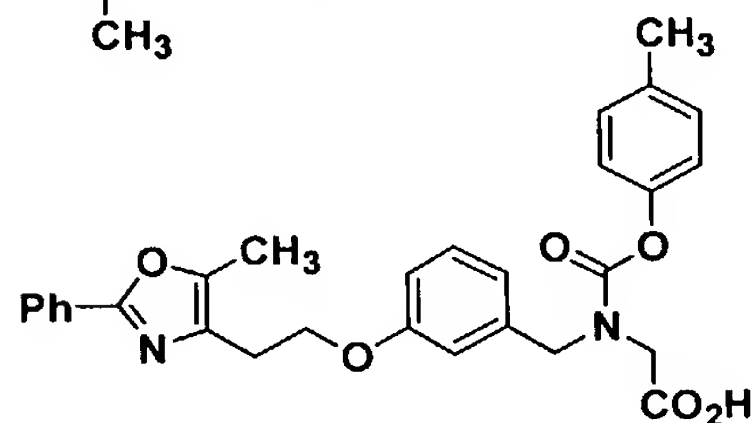
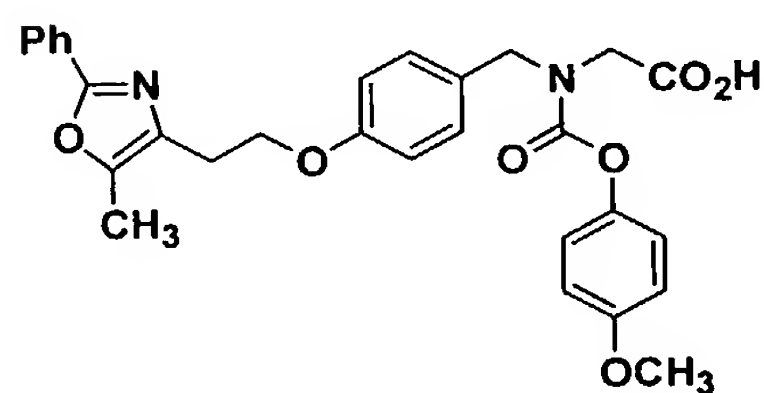
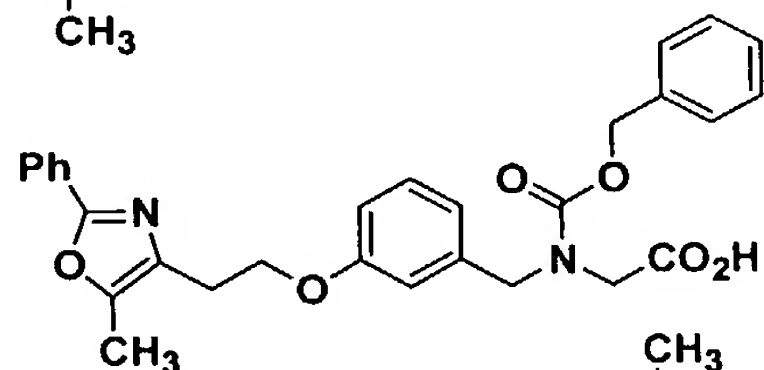
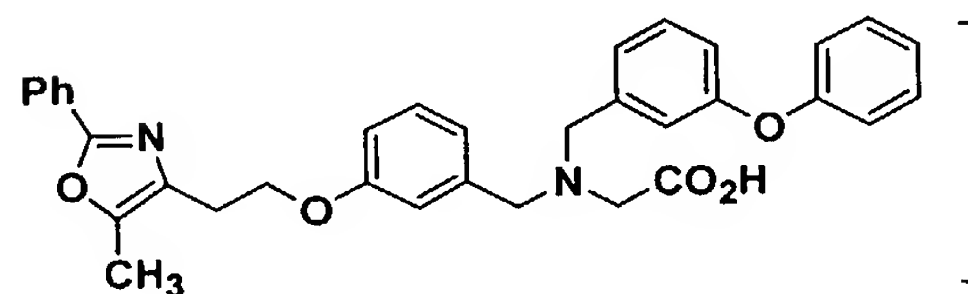
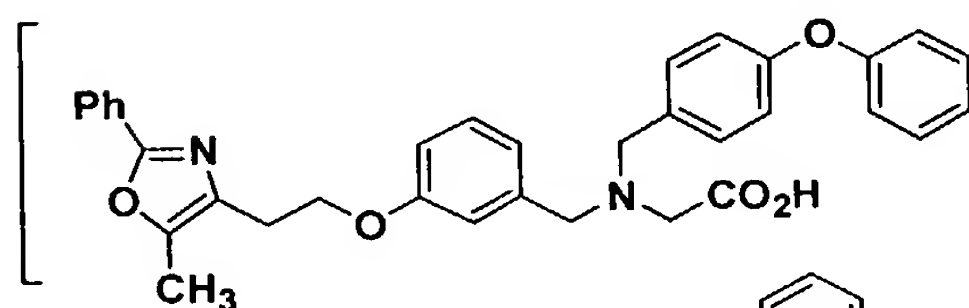
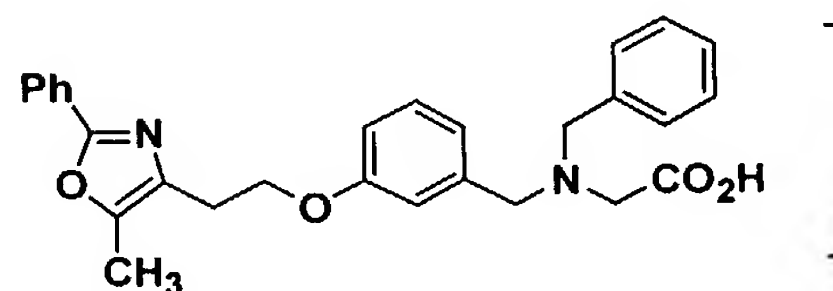
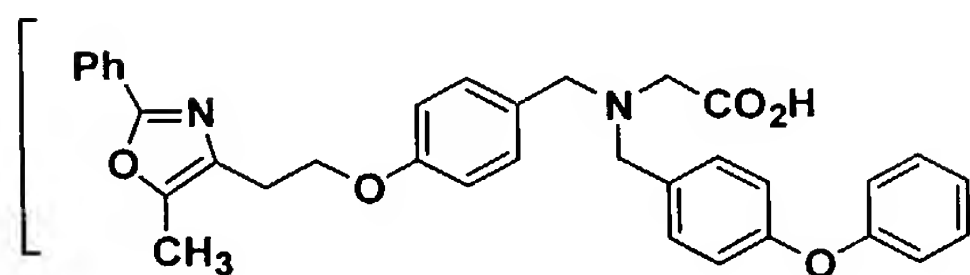
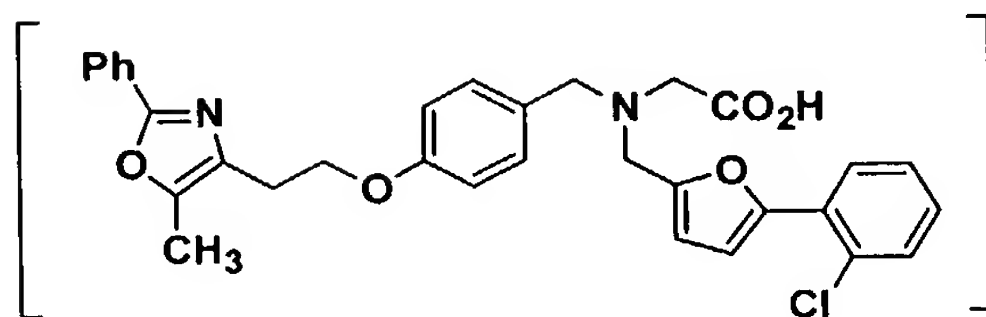


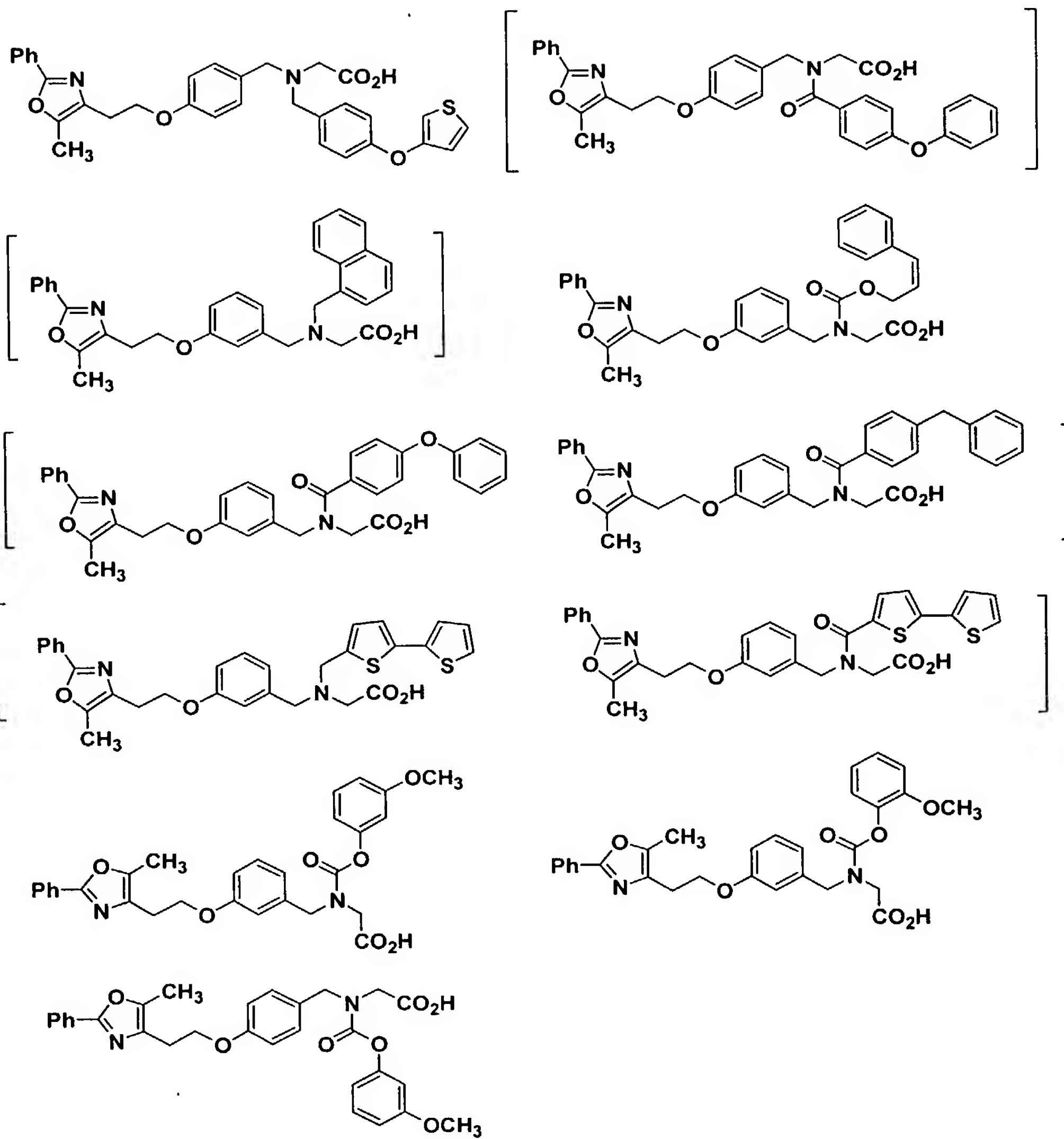


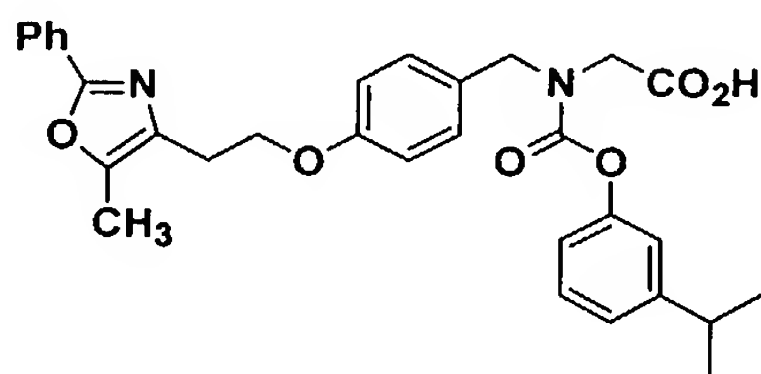
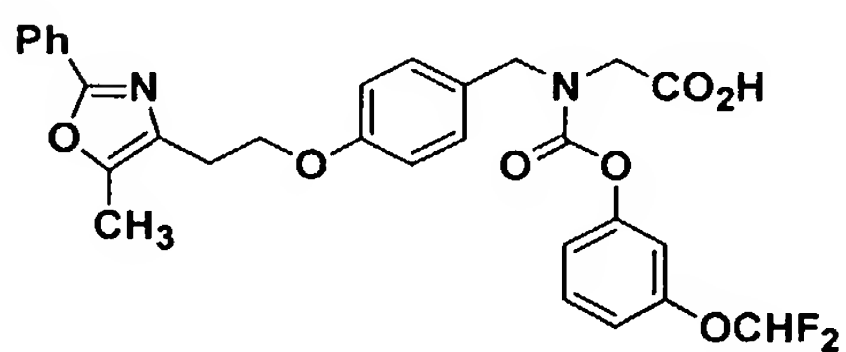
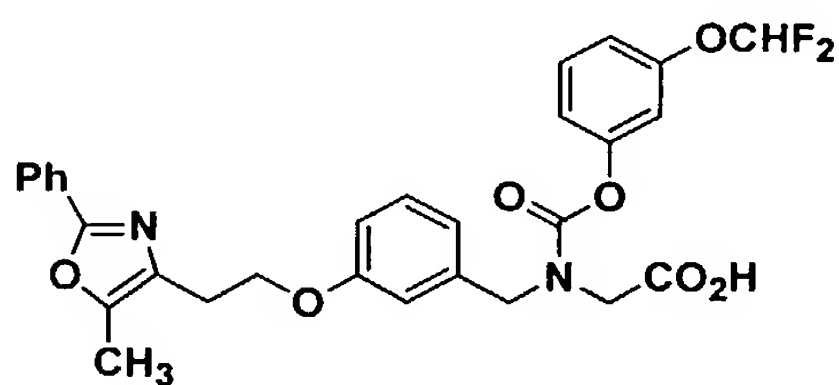
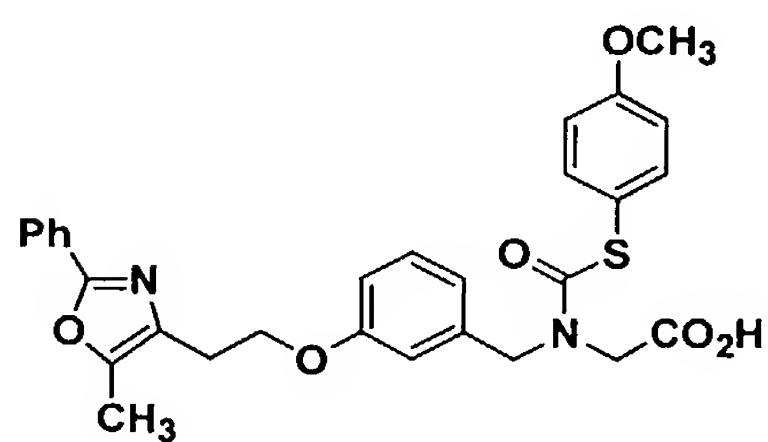
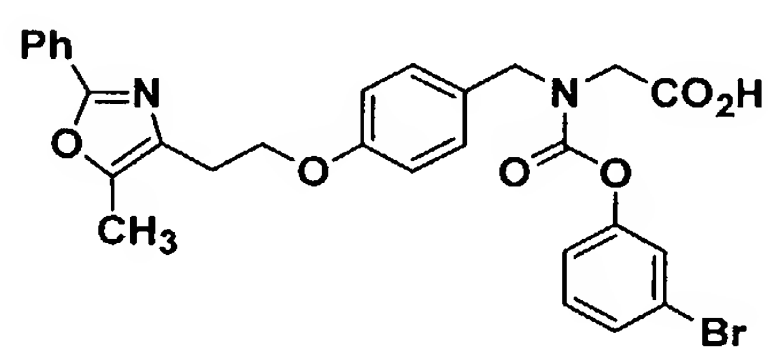
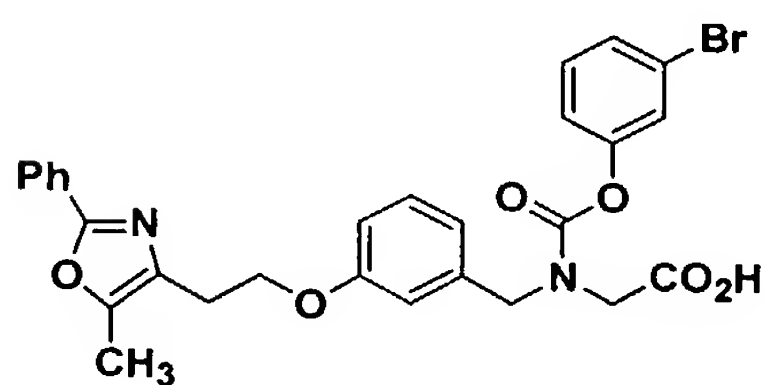
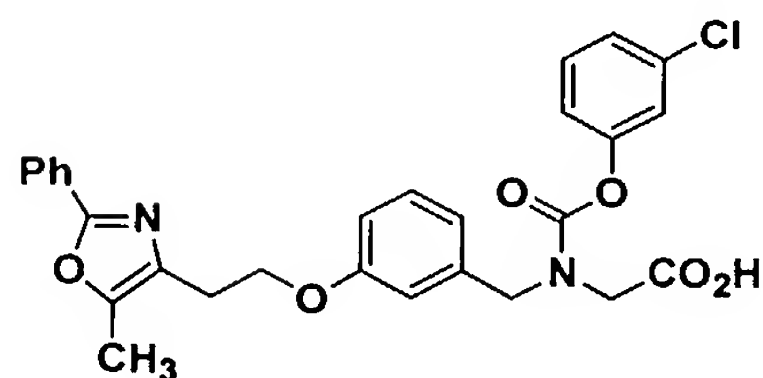
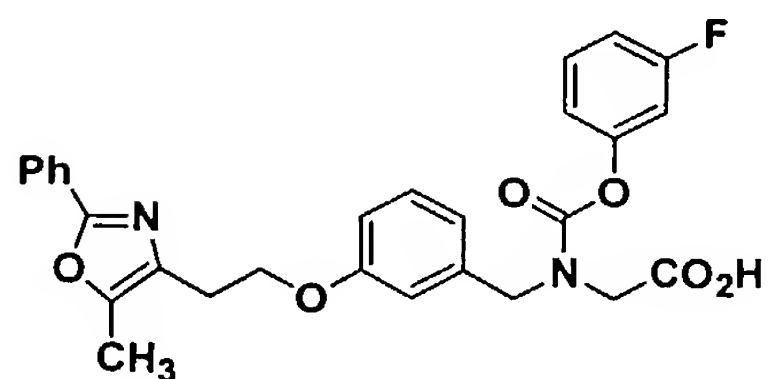
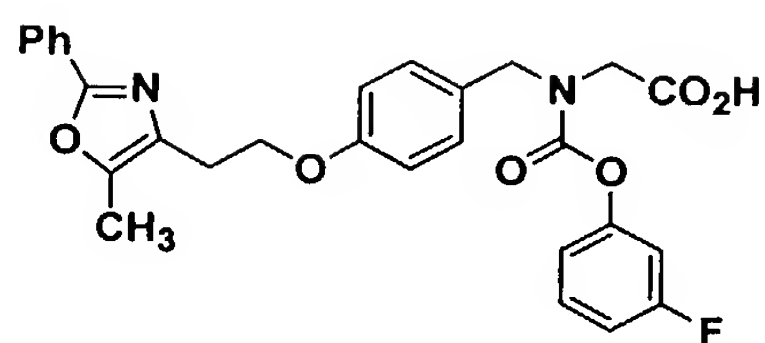
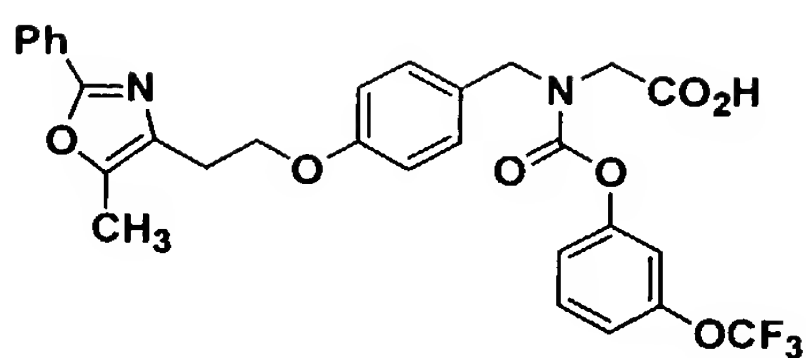
--17. (Amended) The [compound] method as defined in Claim [1] 34 wherein the compound employed has [having] the structure

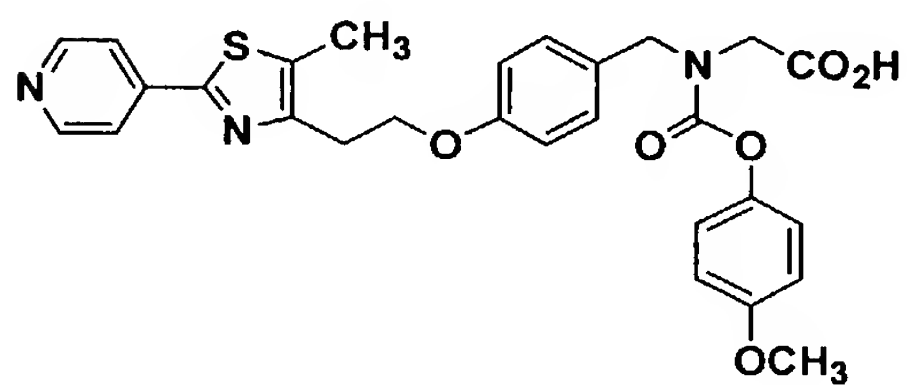
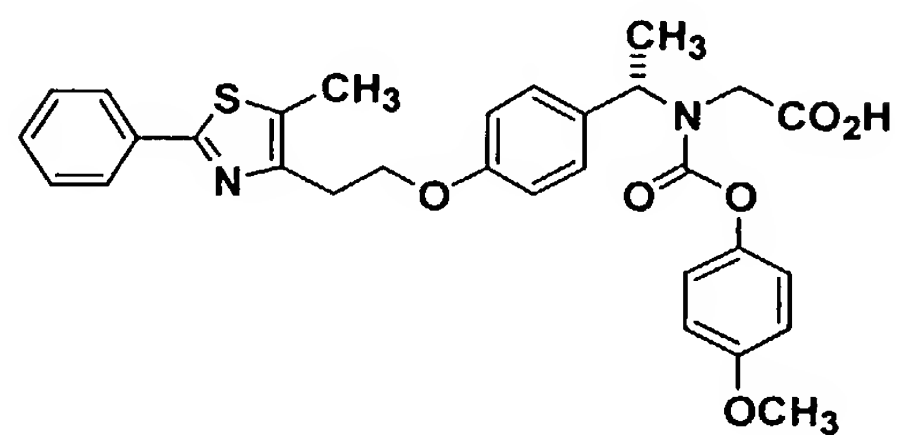
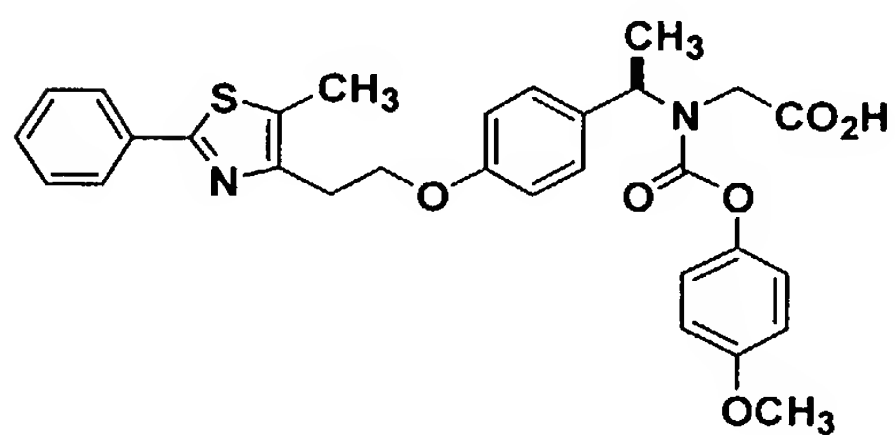
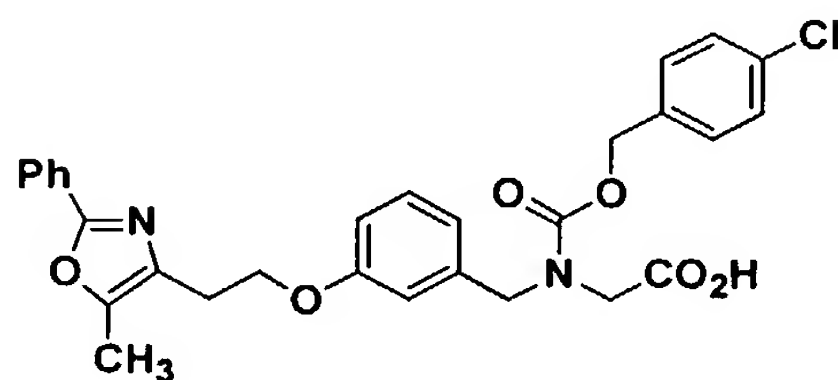
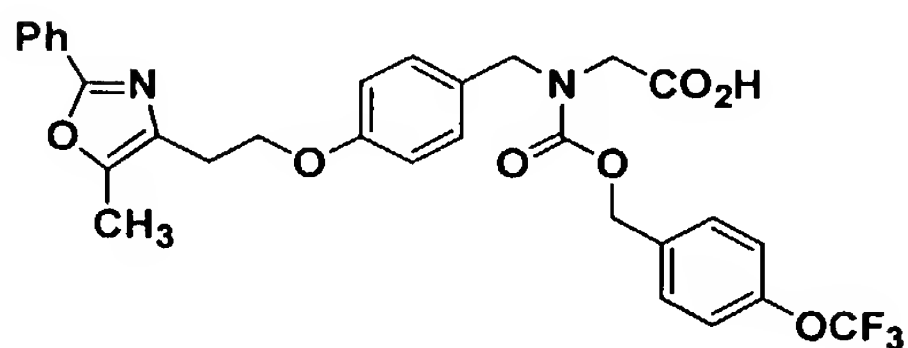
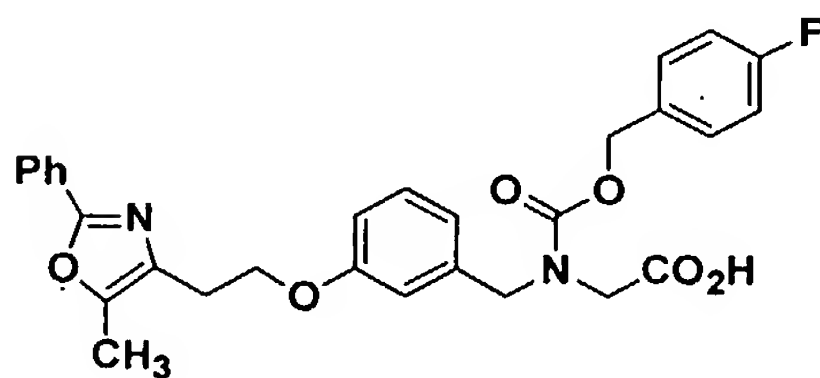
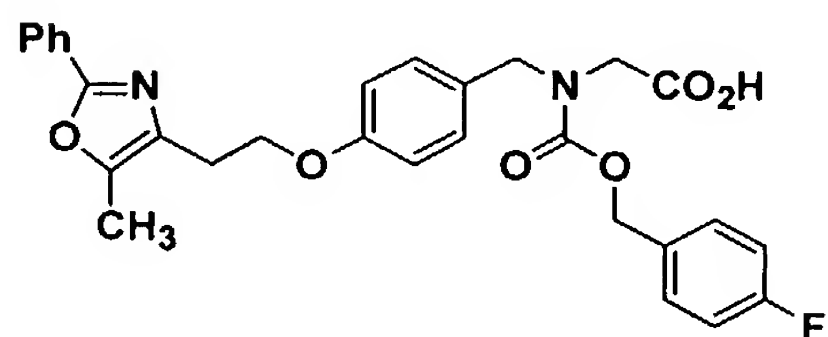
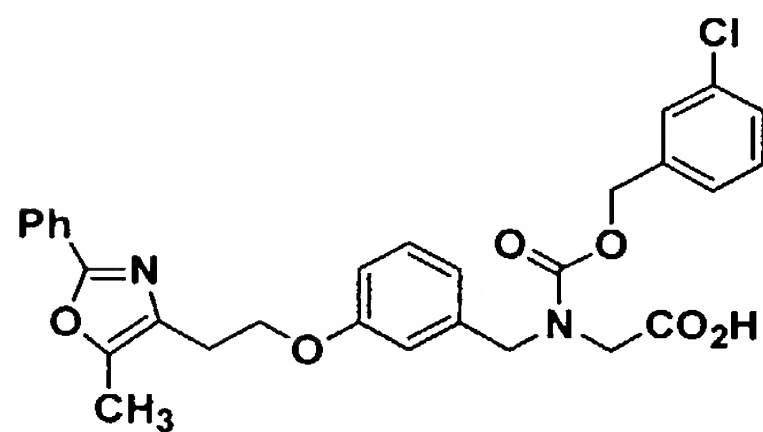
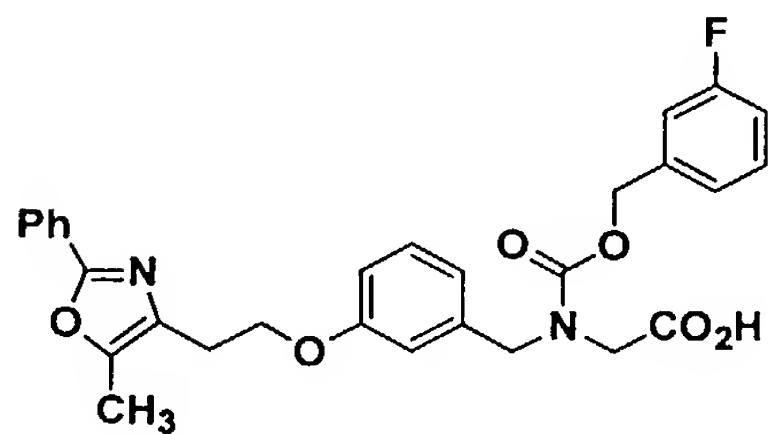
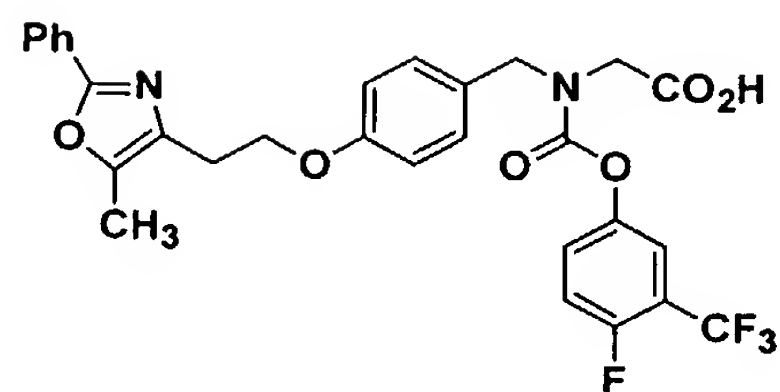
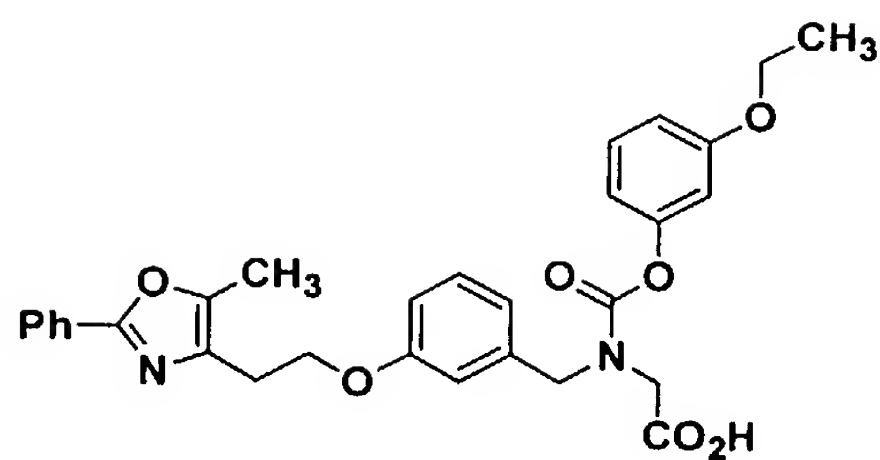






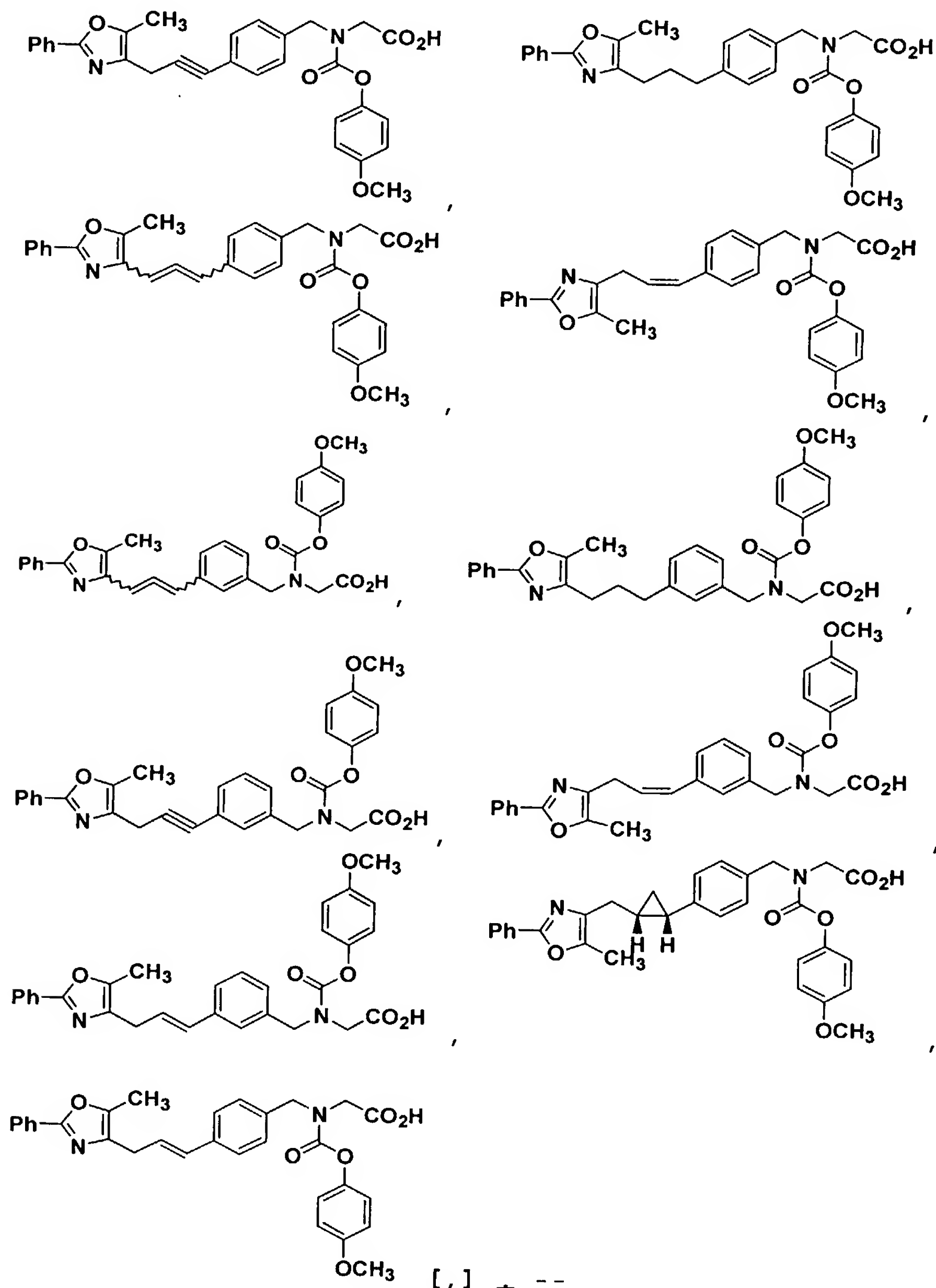


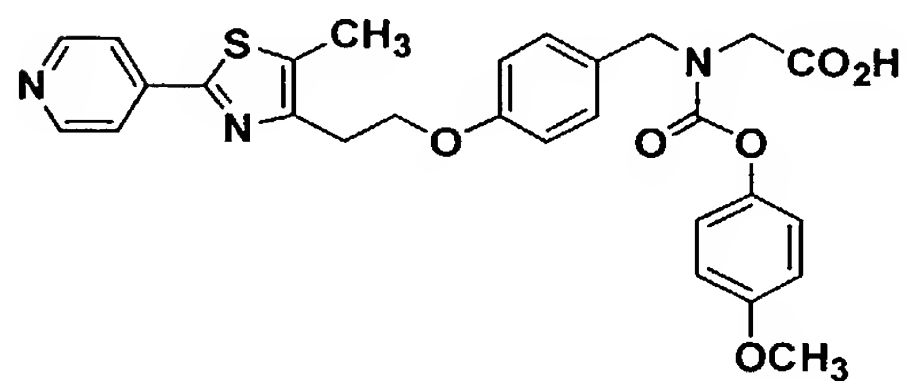
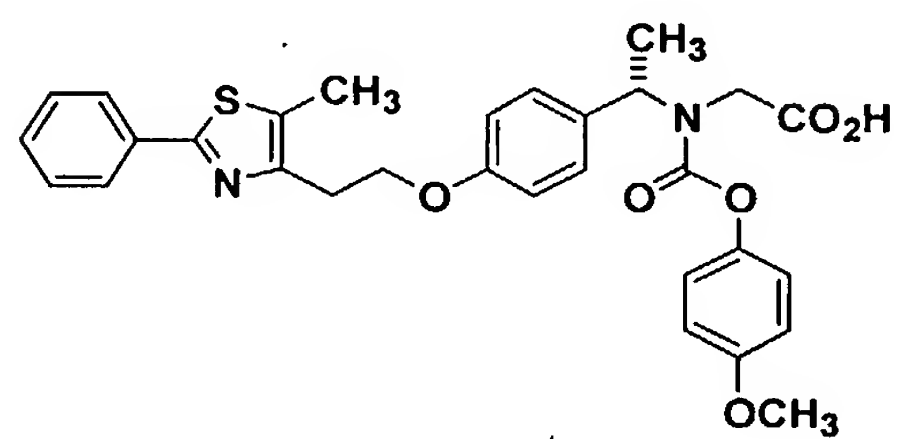
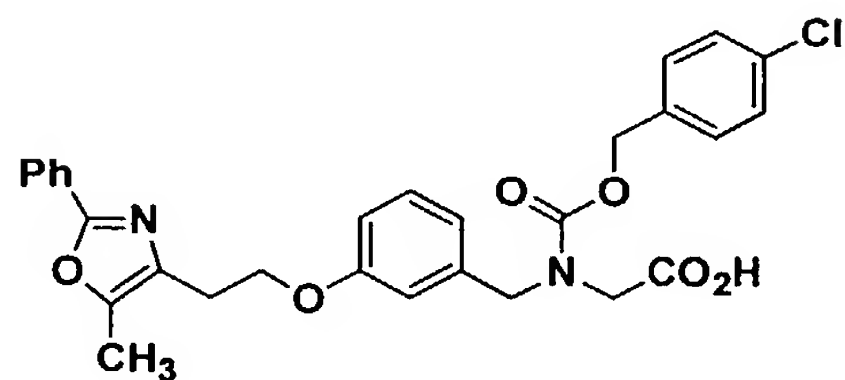
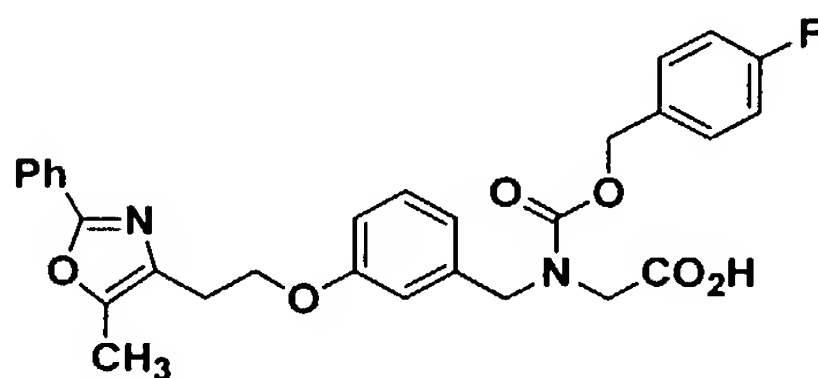
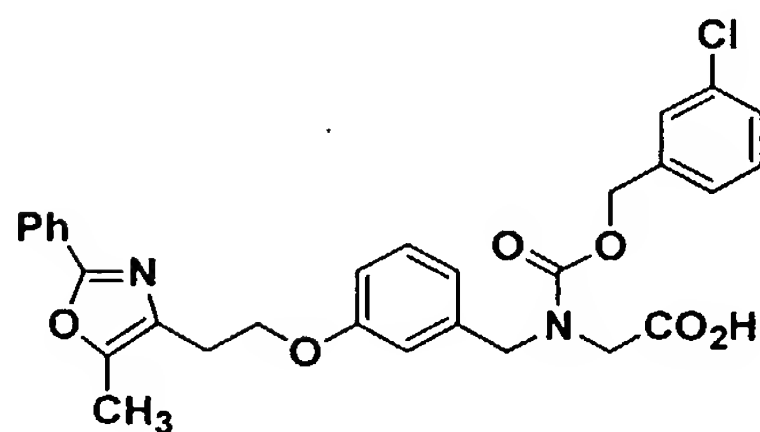
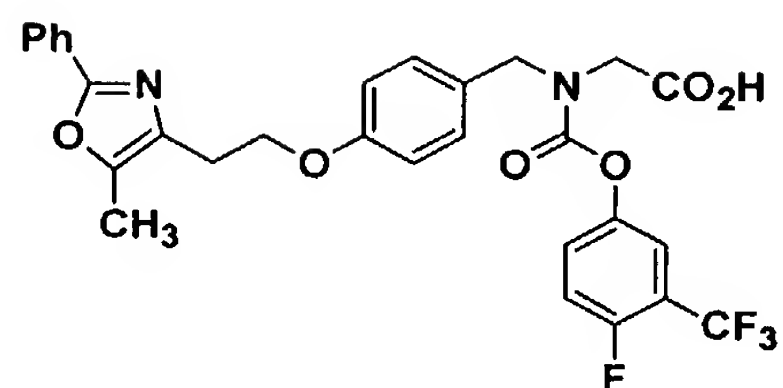




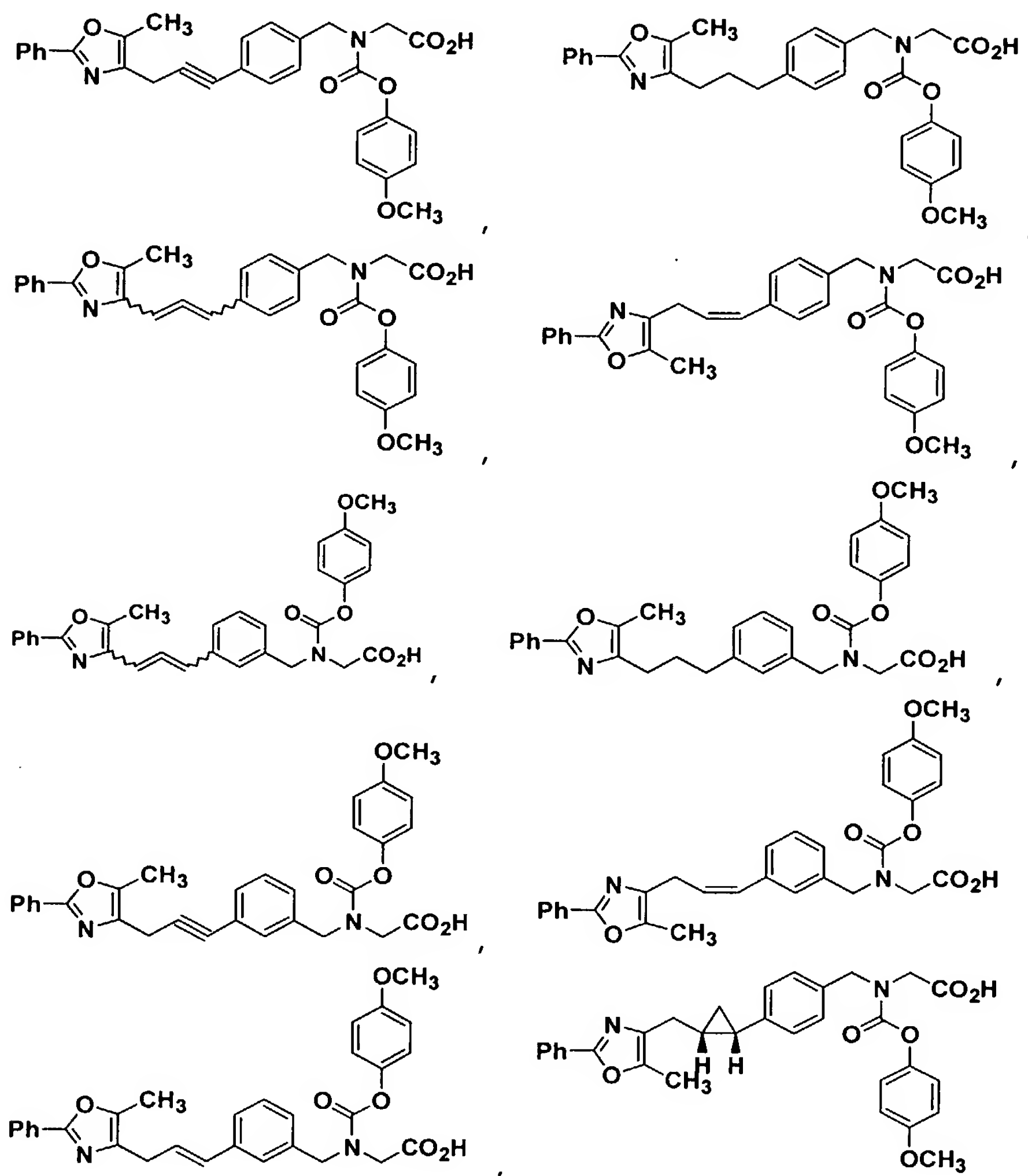


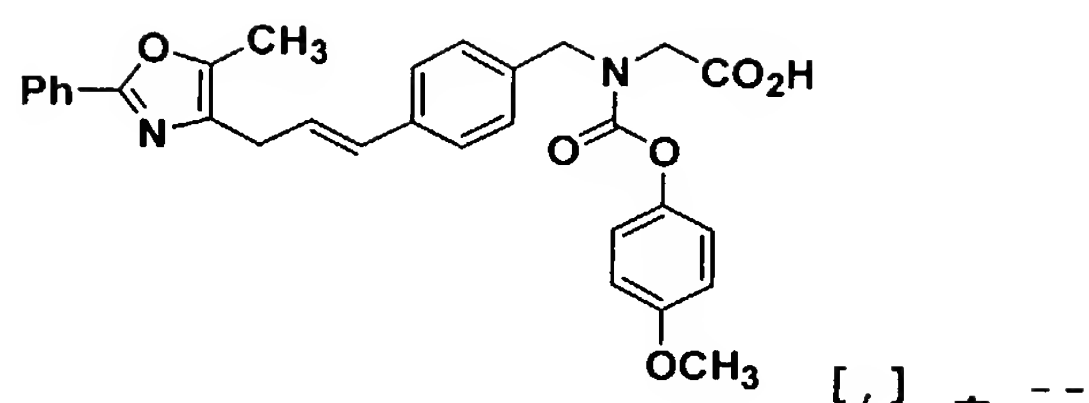
18. The [compound] method as defined in Claim 34 [1 having] wherein the compound employed has the structure



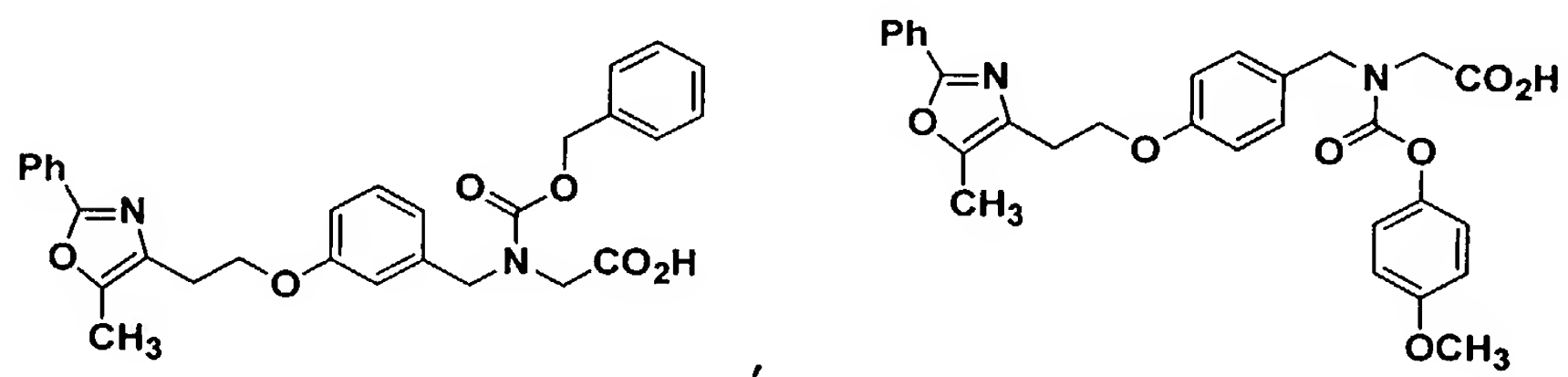
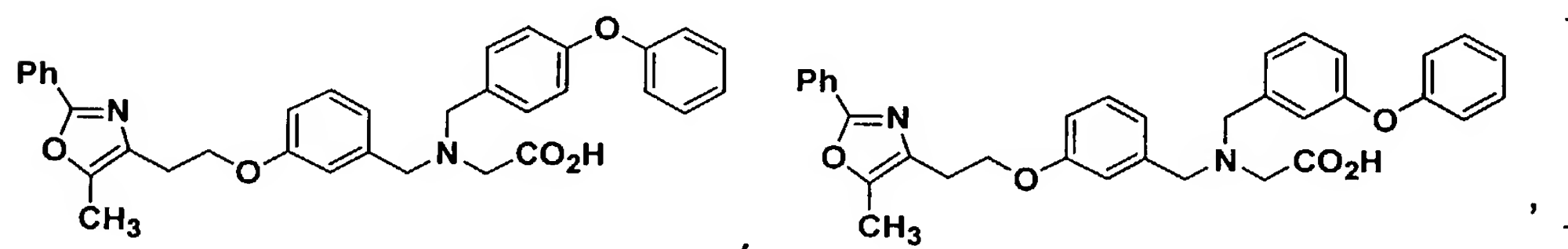
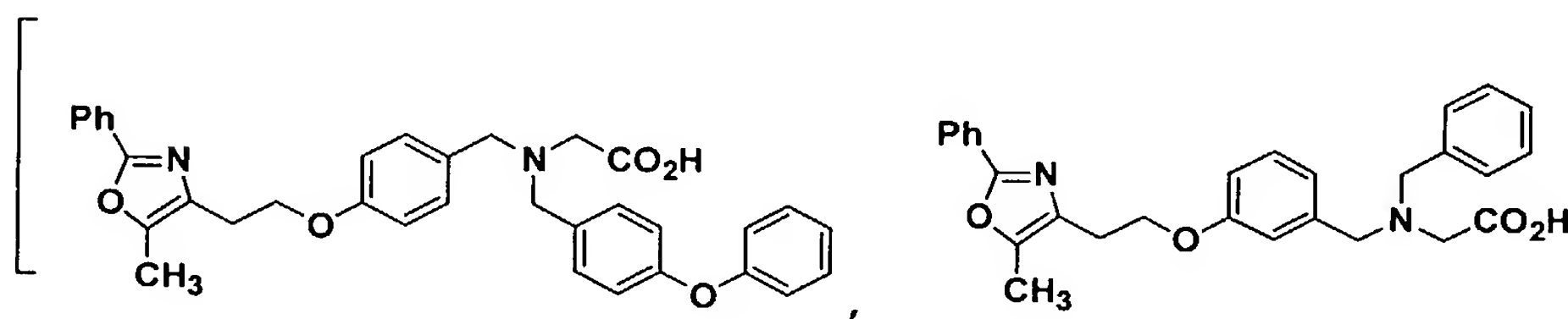
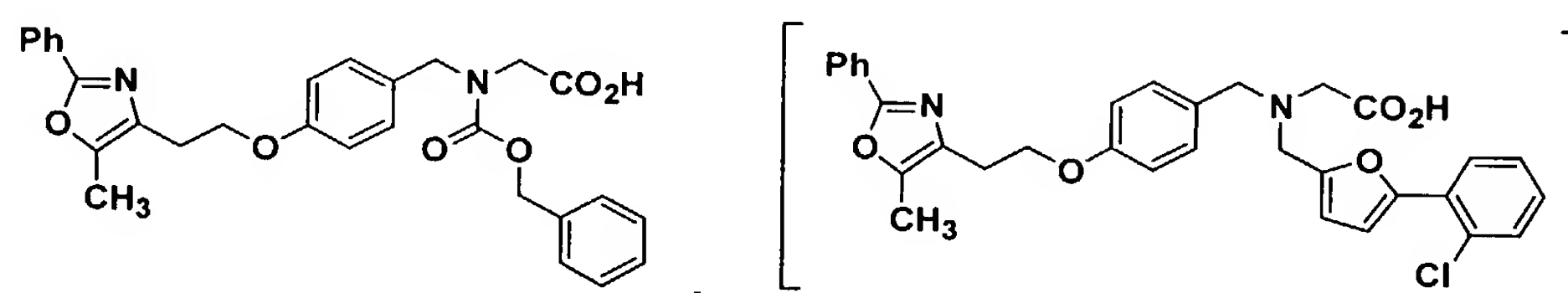


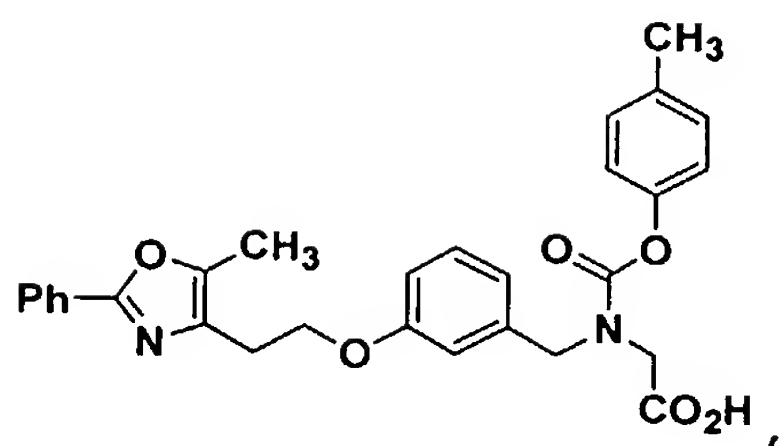
18. The [compound] method as defined in Claim 34 [1 having] wherein the compound employed has the structure

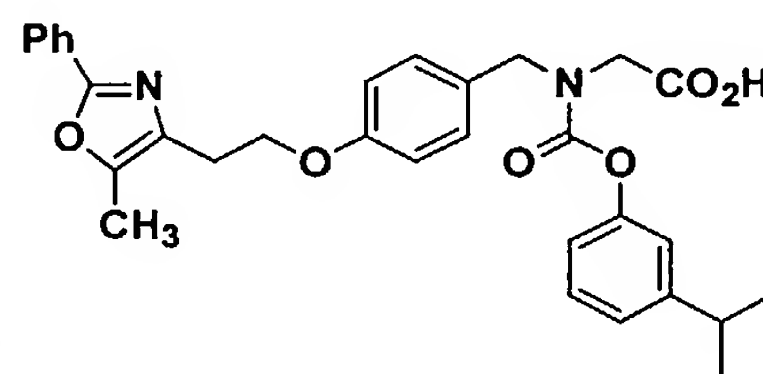
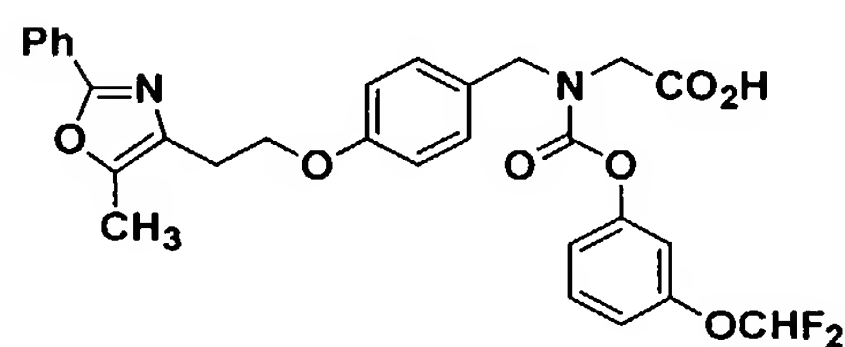
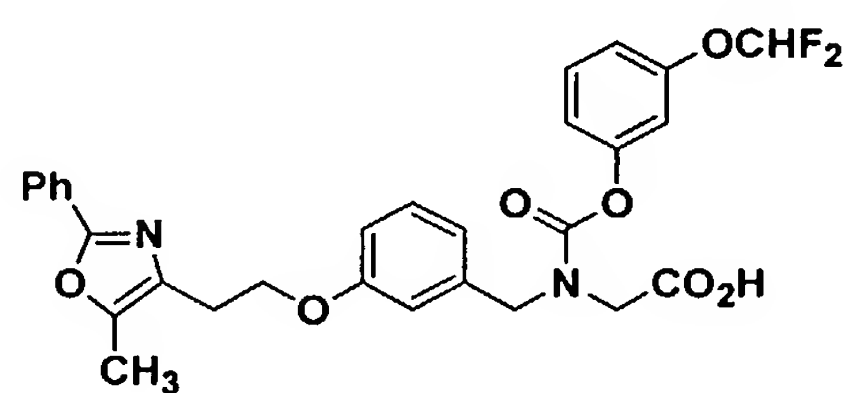
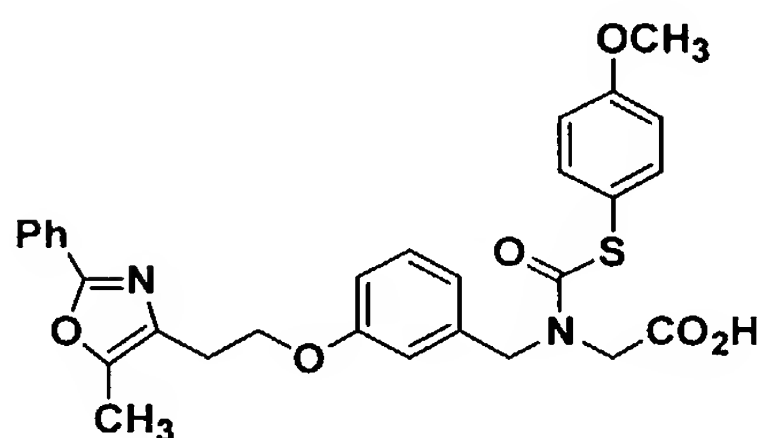
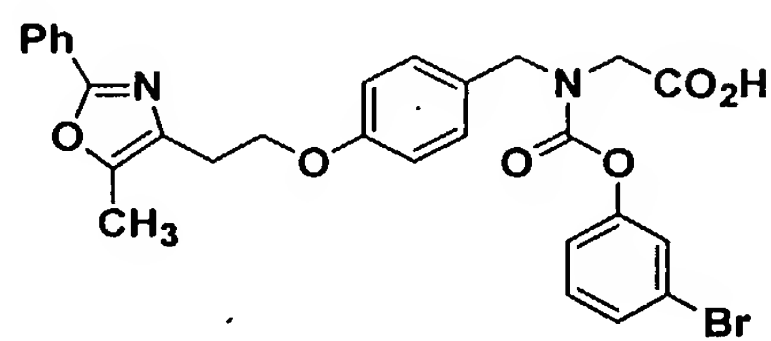
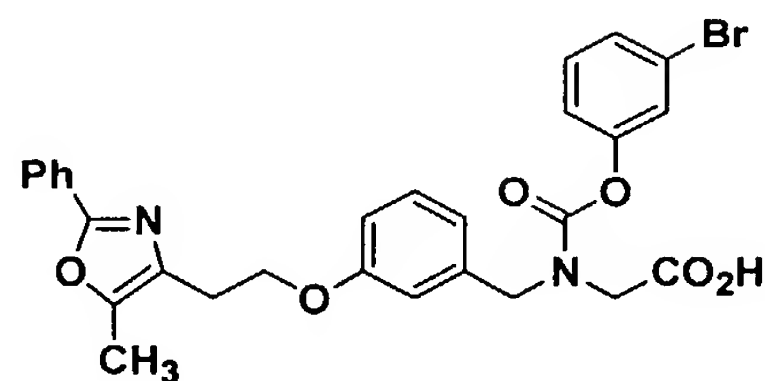
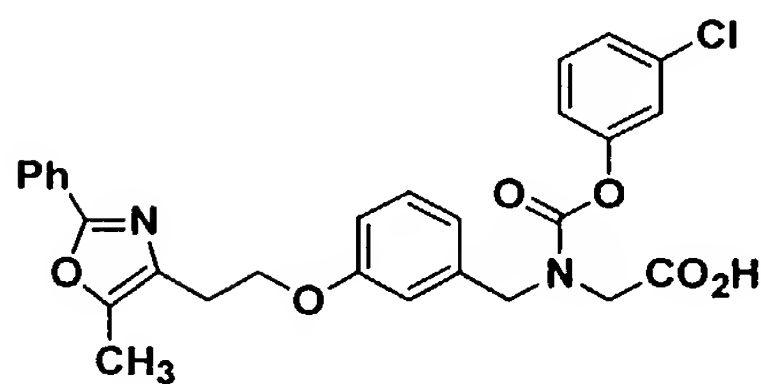
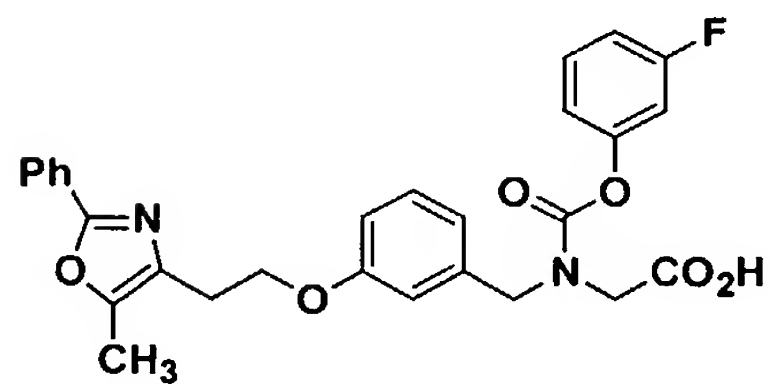
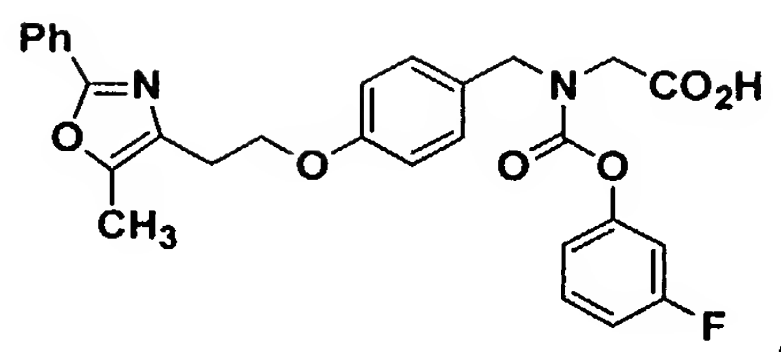
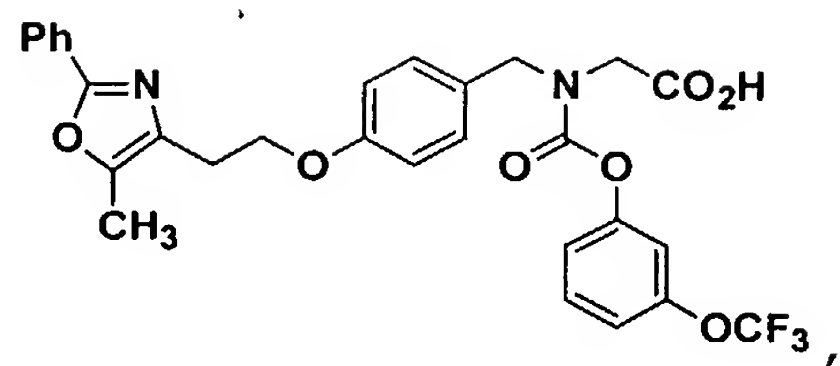


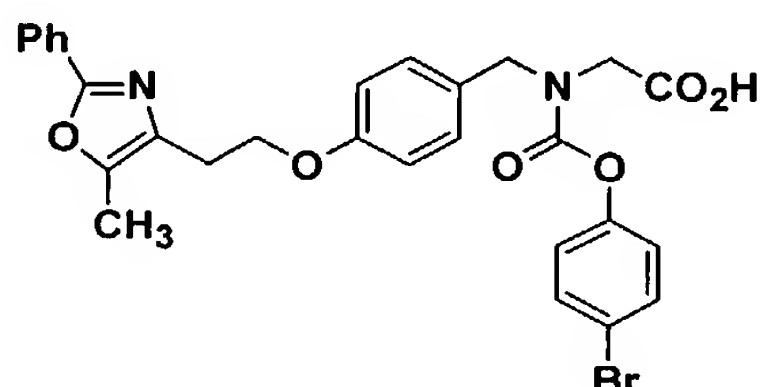
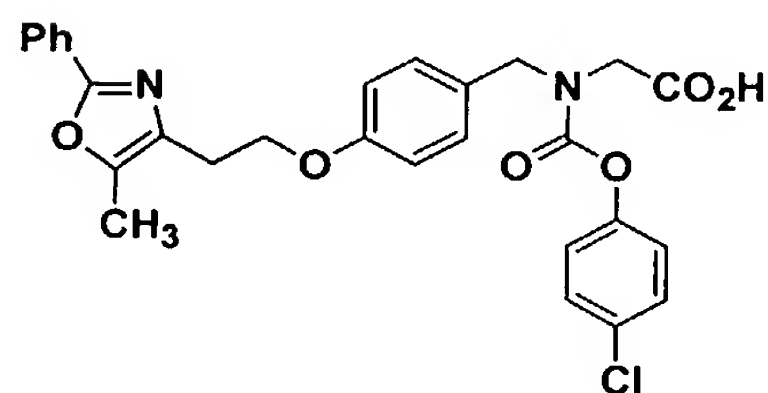
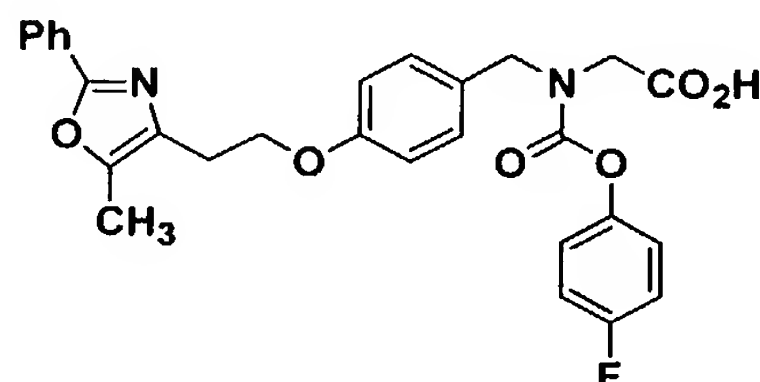
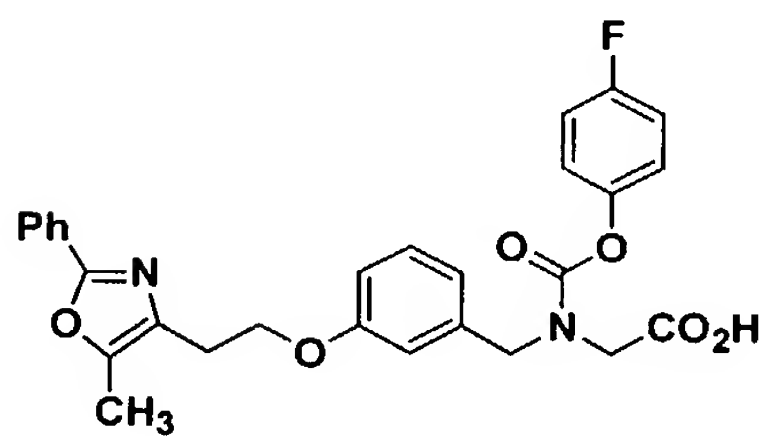
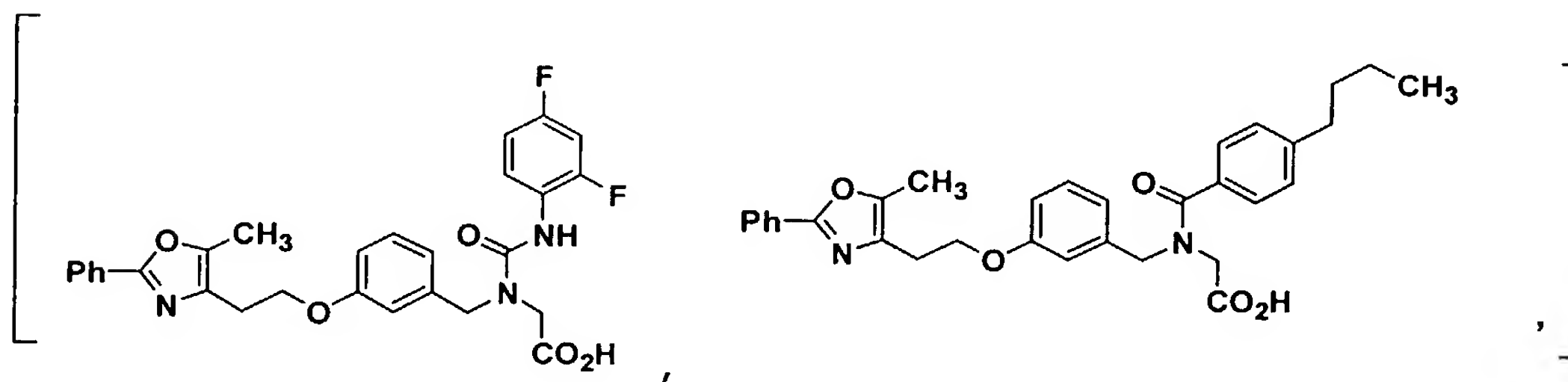
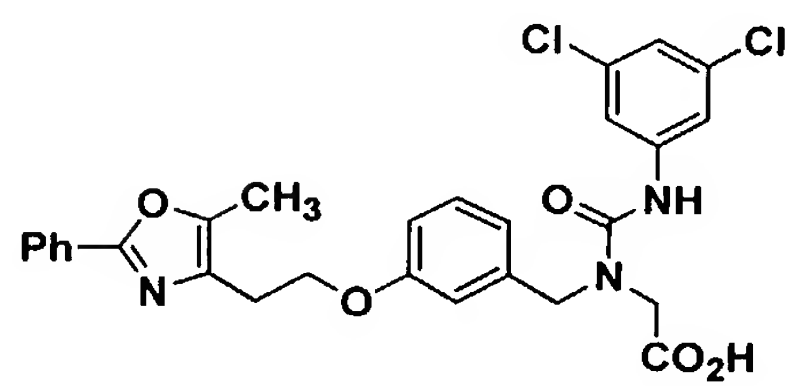
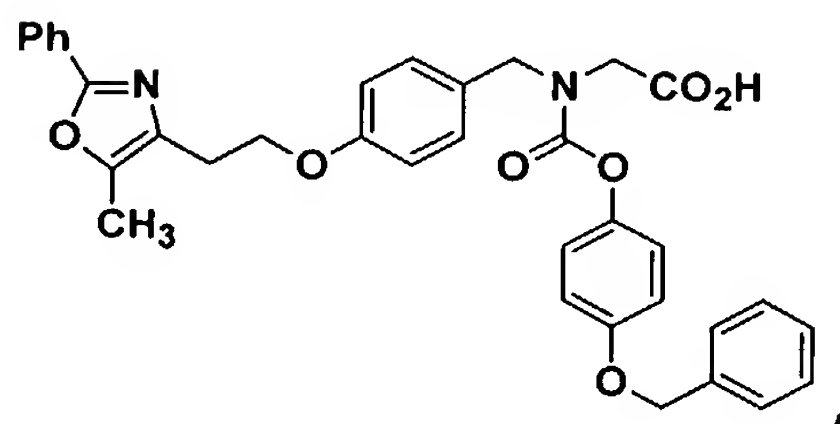
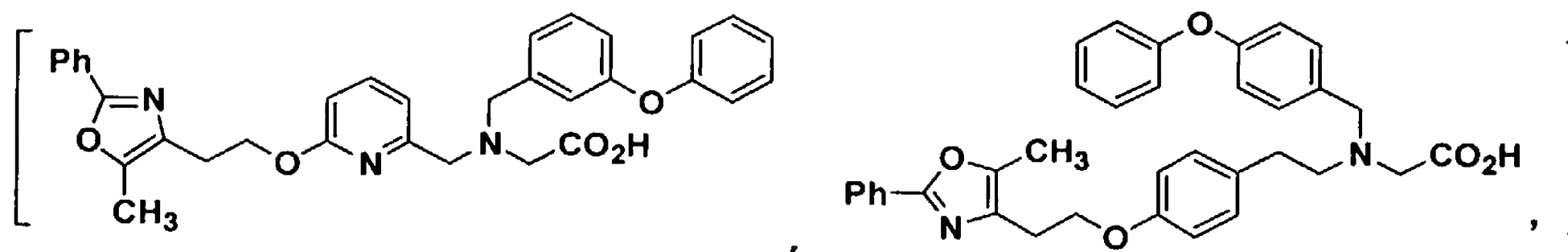


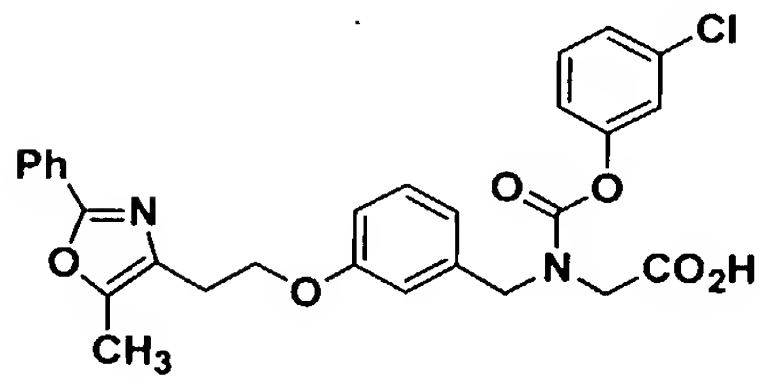
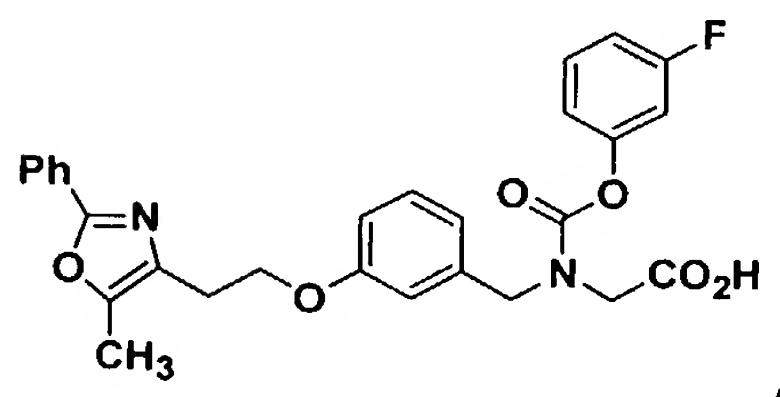
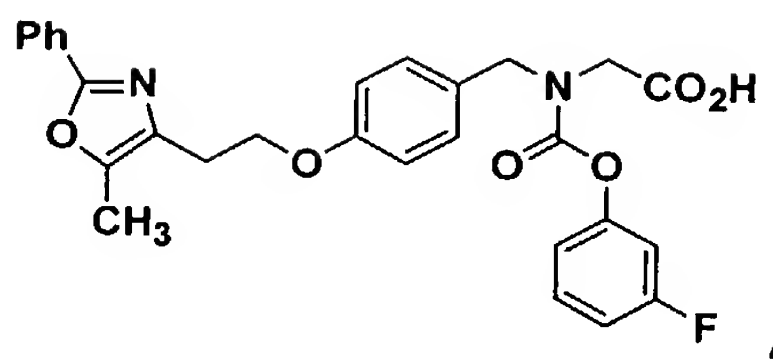
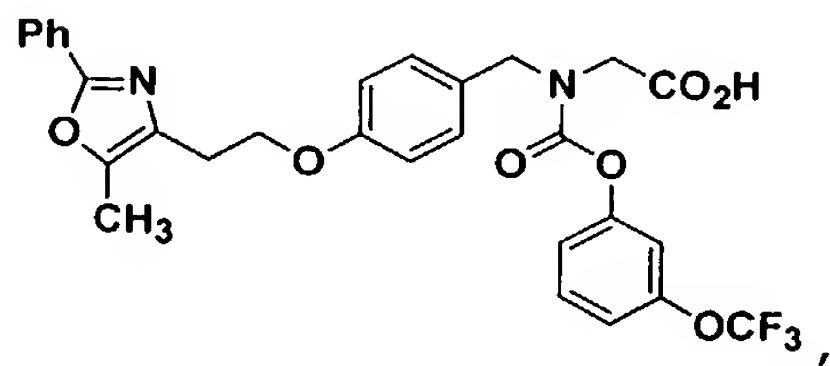
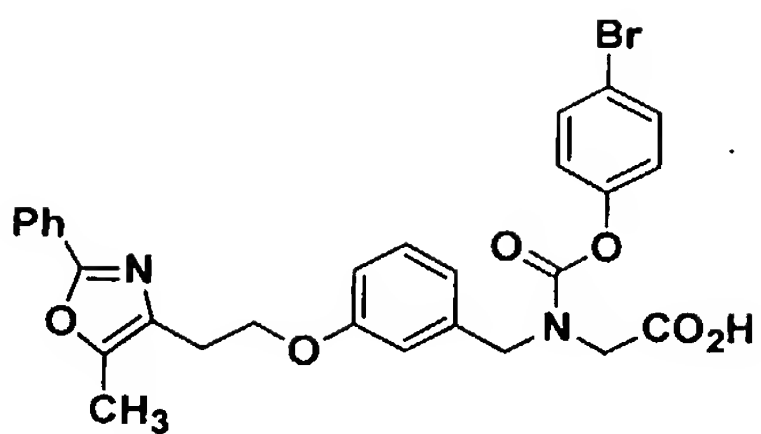
--20. (Amended) The [compound] method as defined in Claim [1] 34 wherein the compound employed has [having] the structure



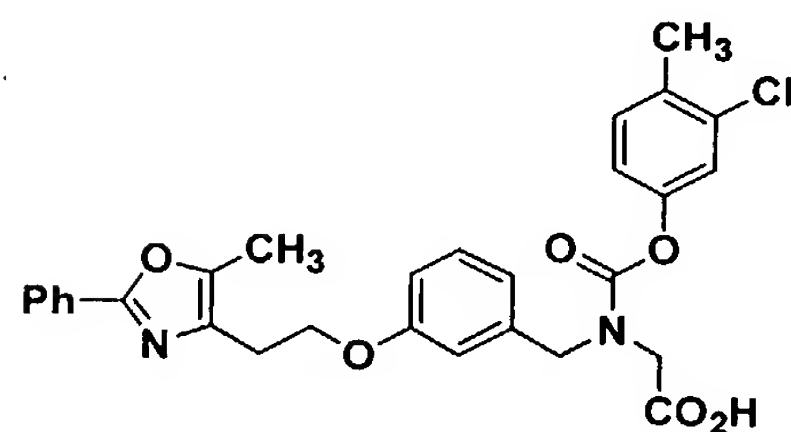
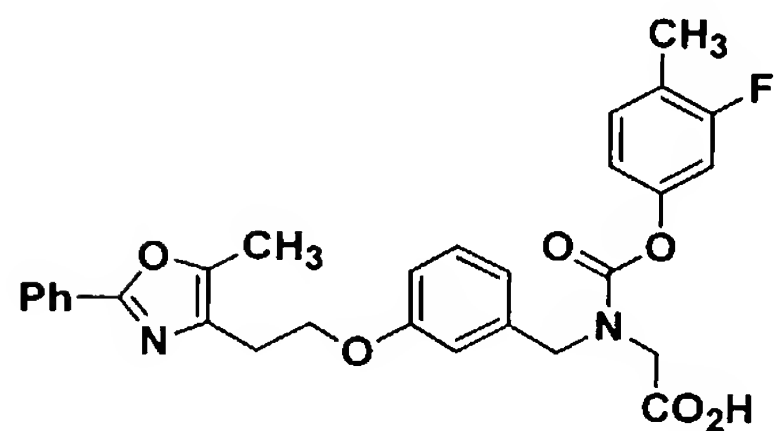
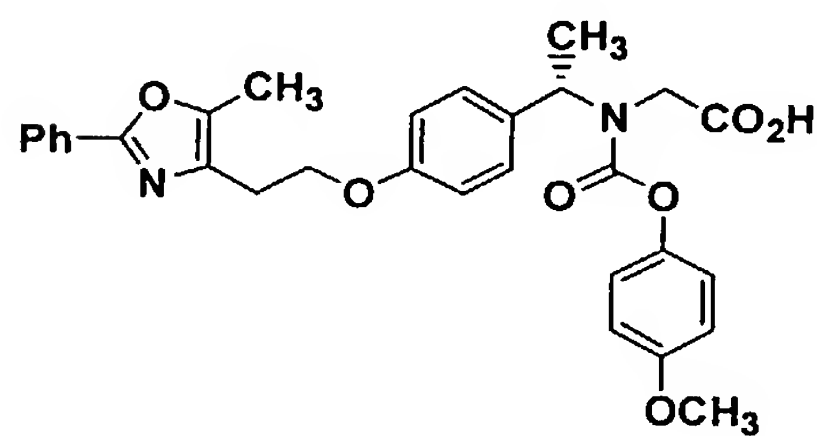
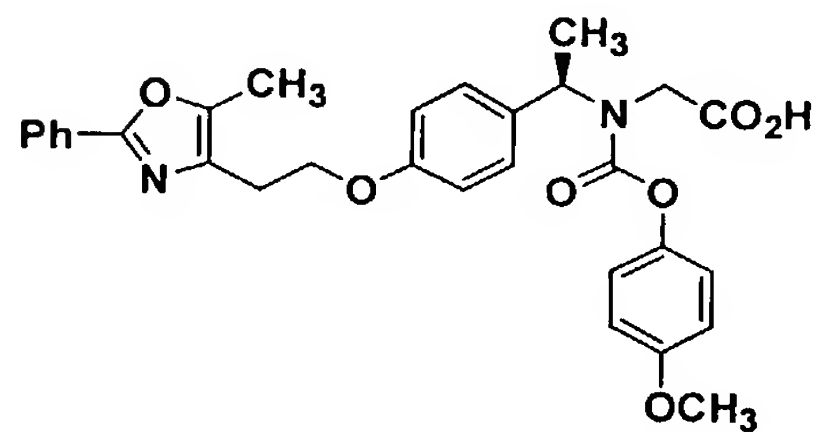
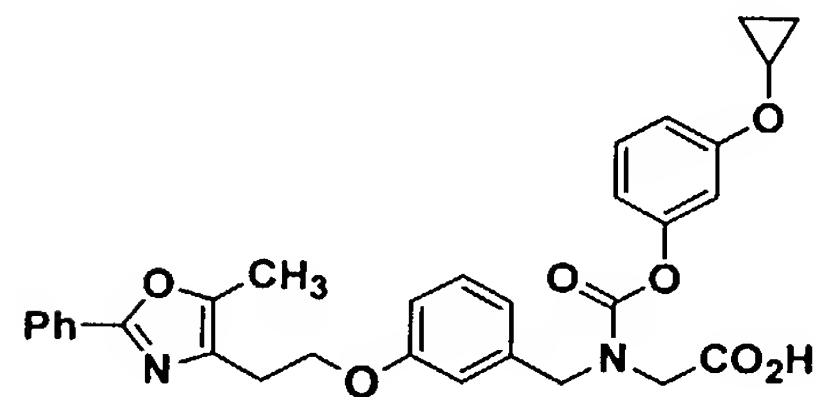
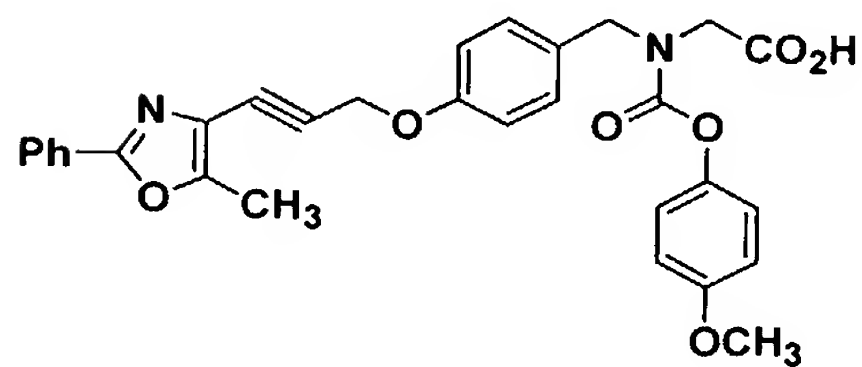
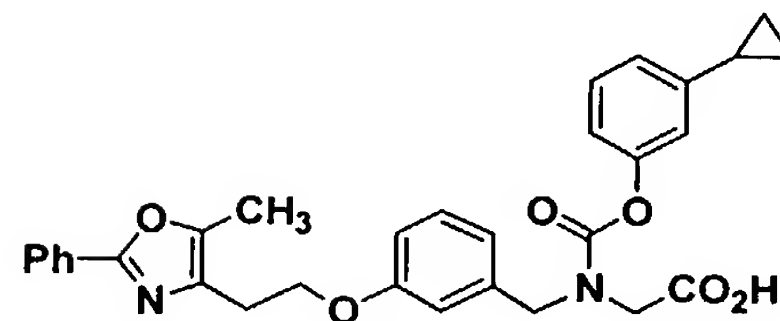
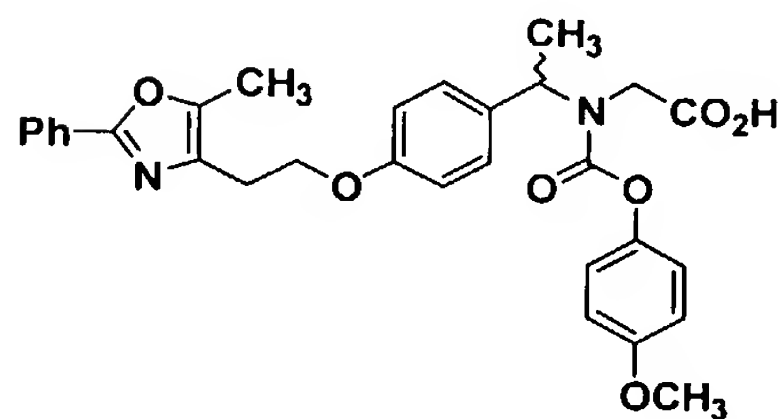
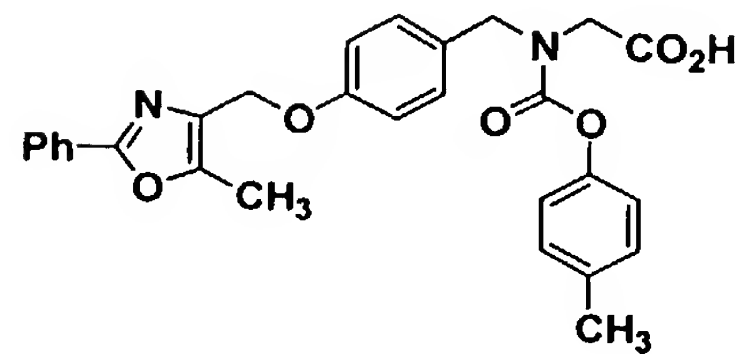
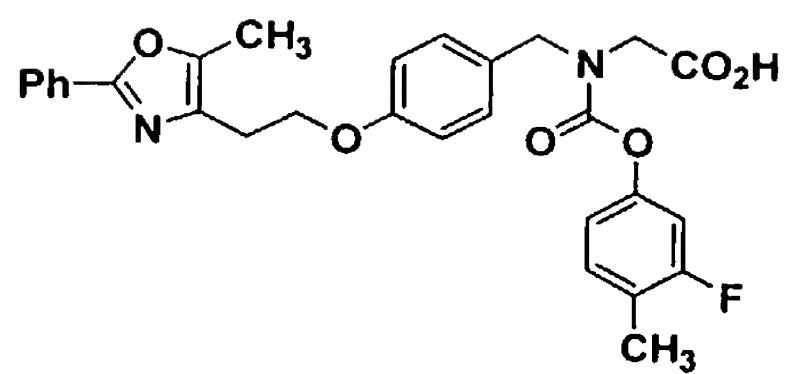


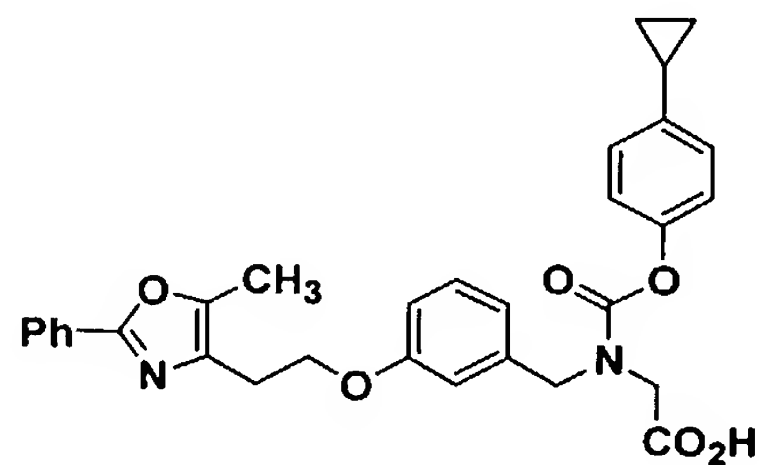
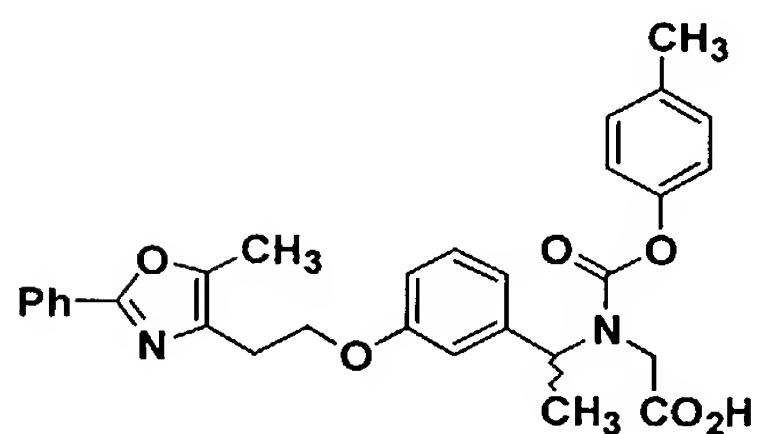
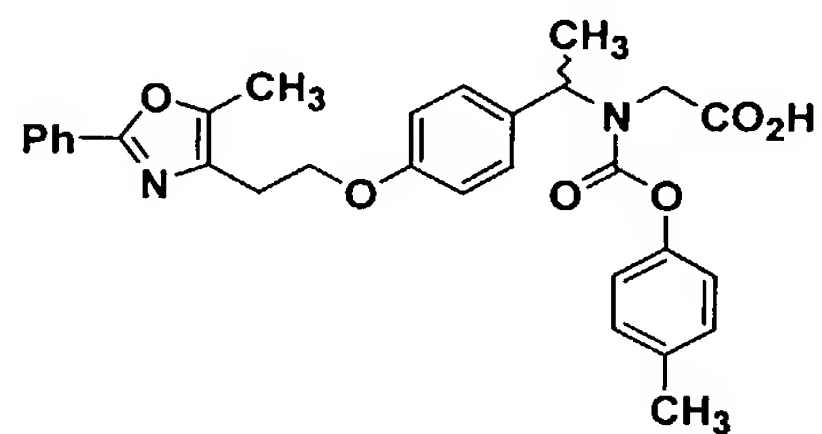
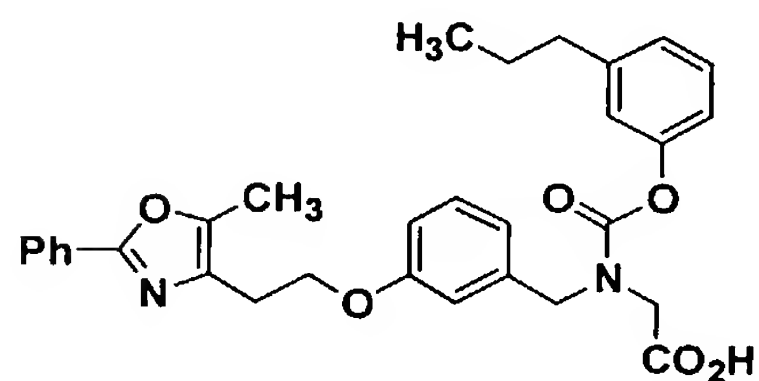
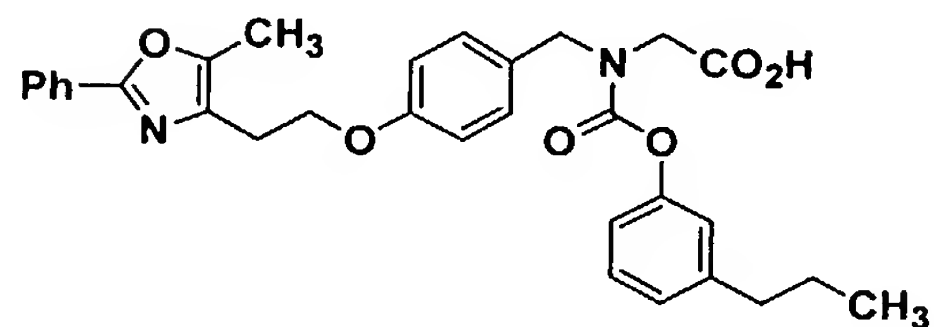
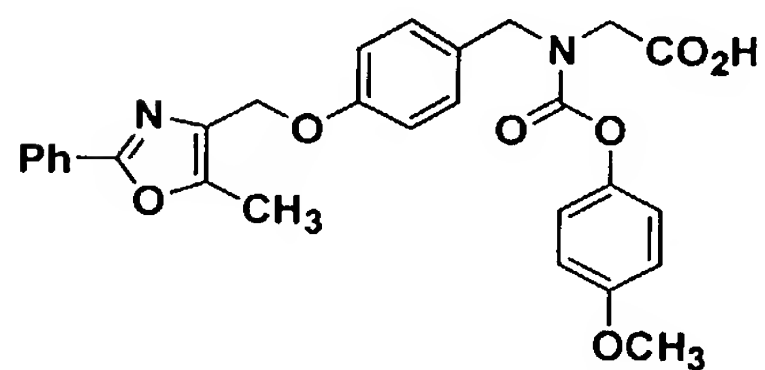
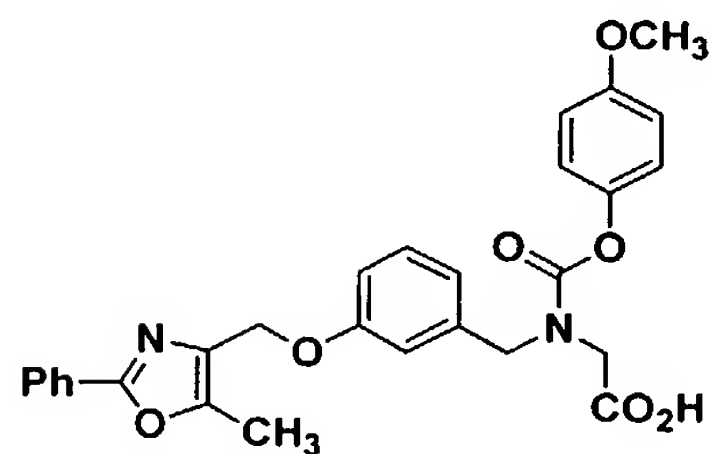
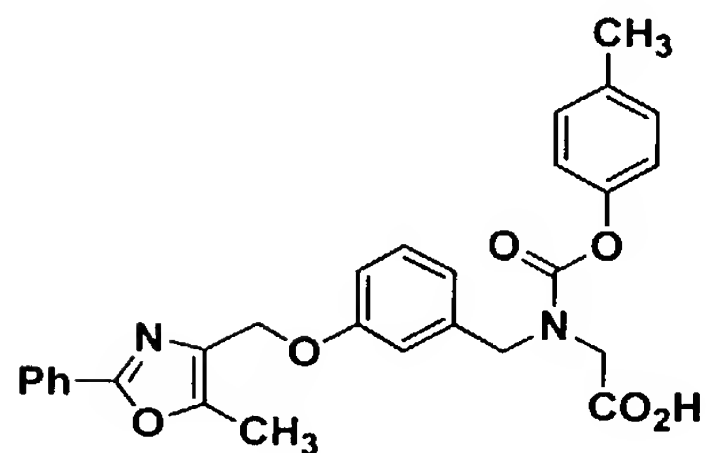
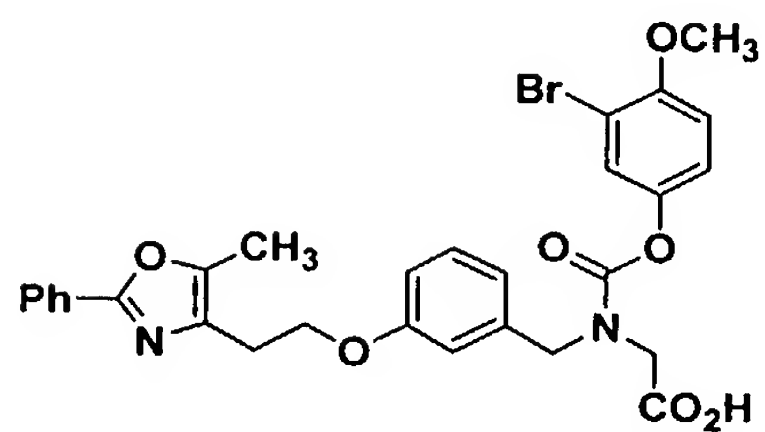
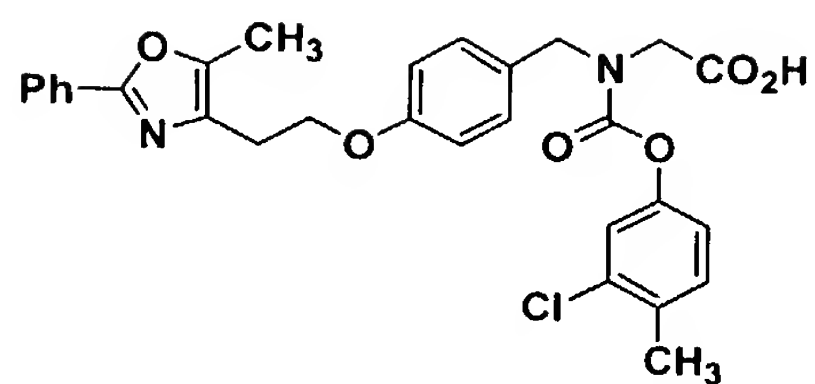




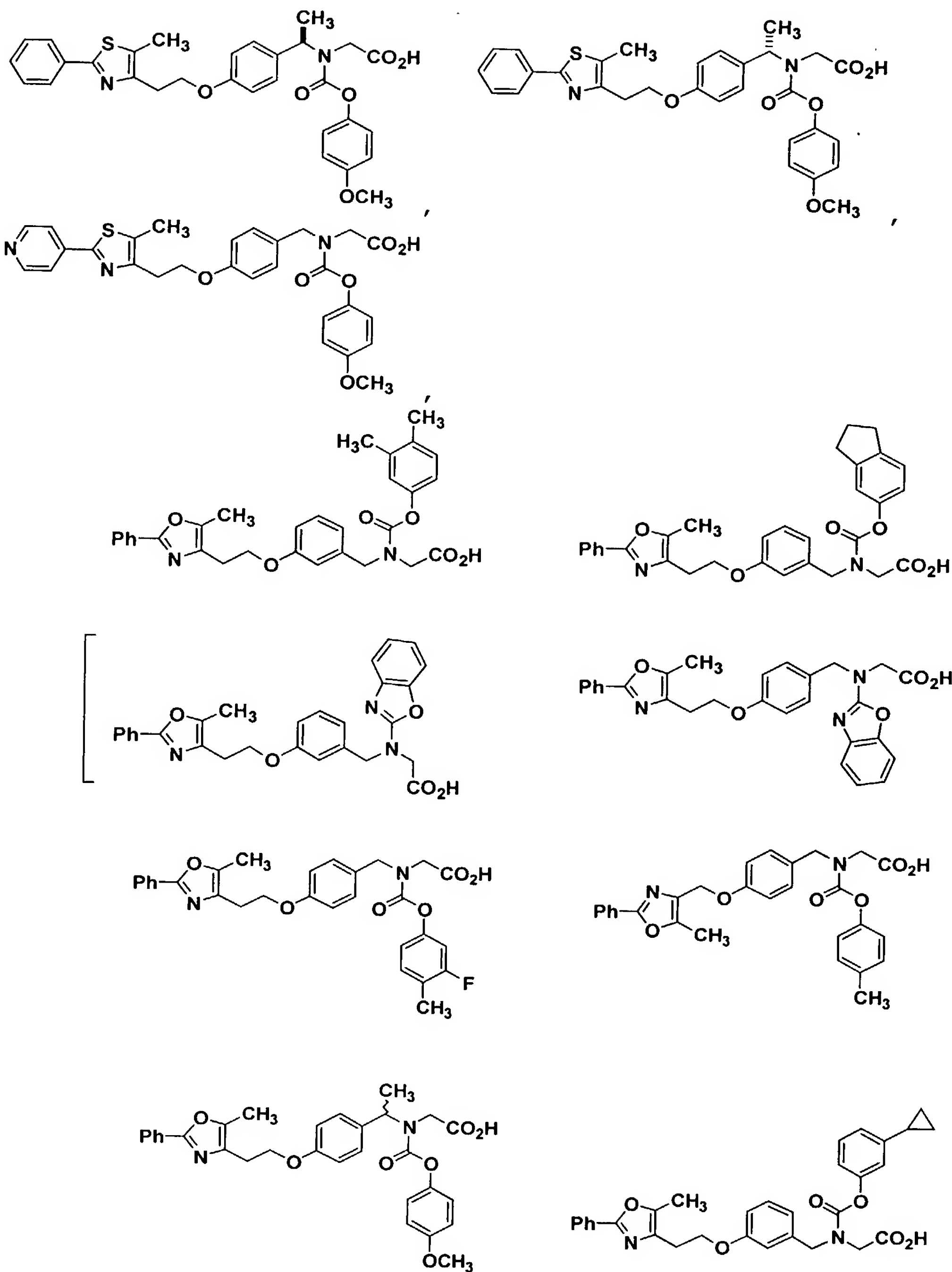




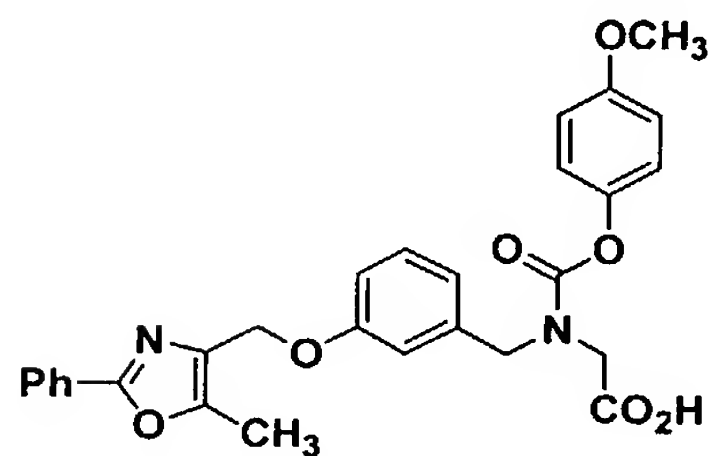
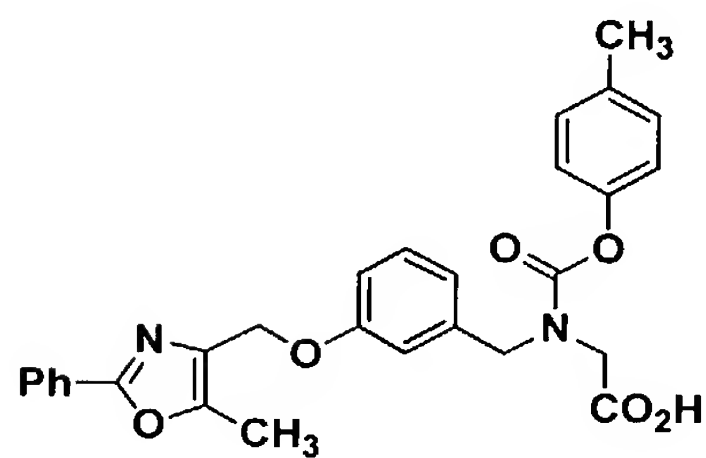
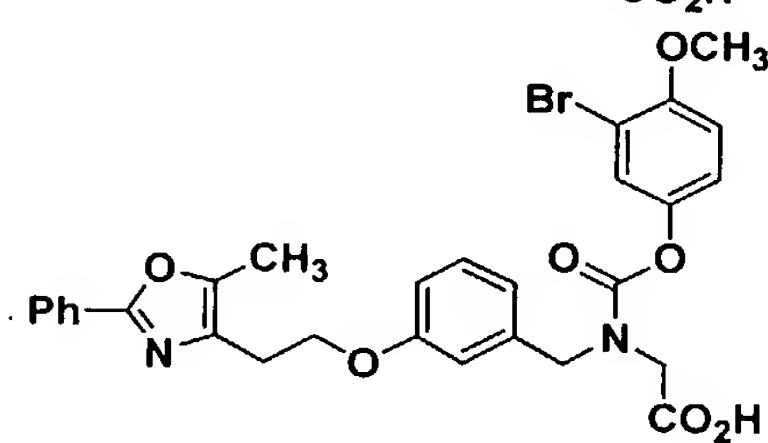
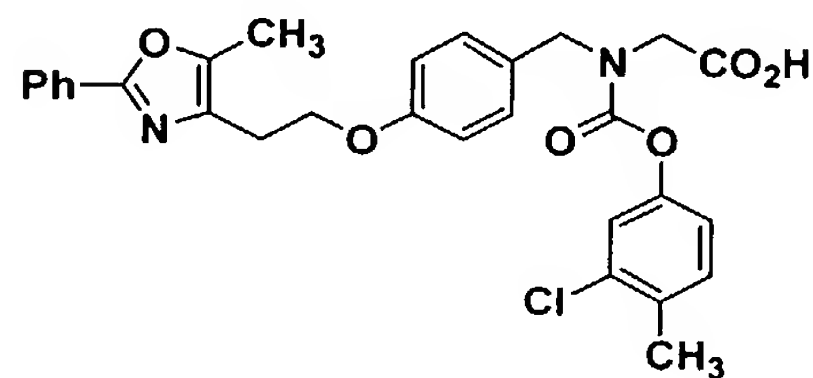
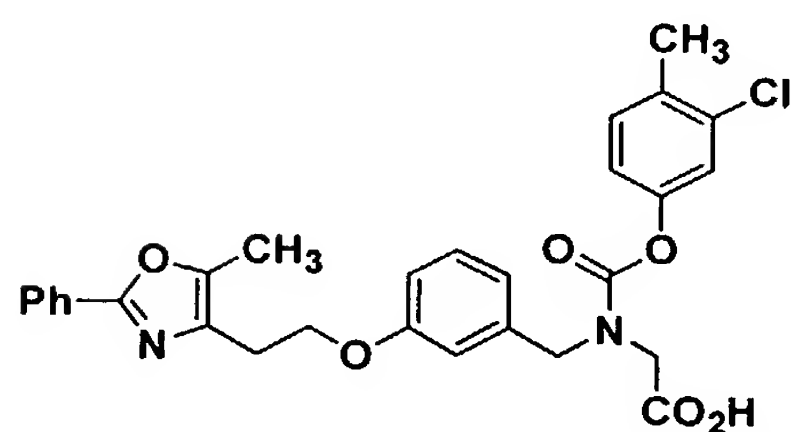
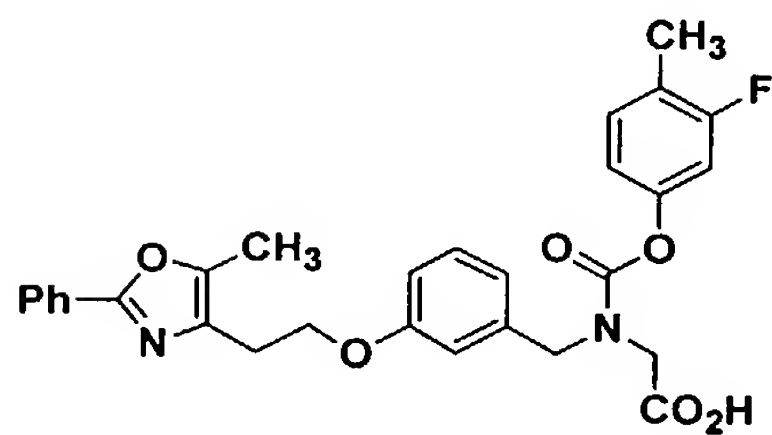
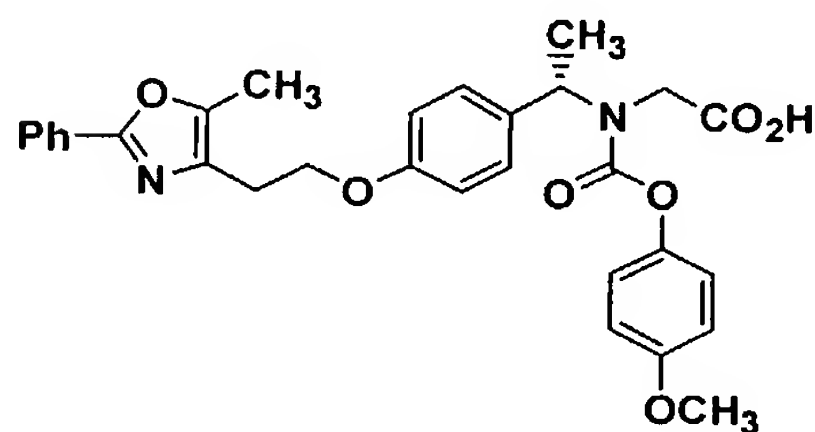
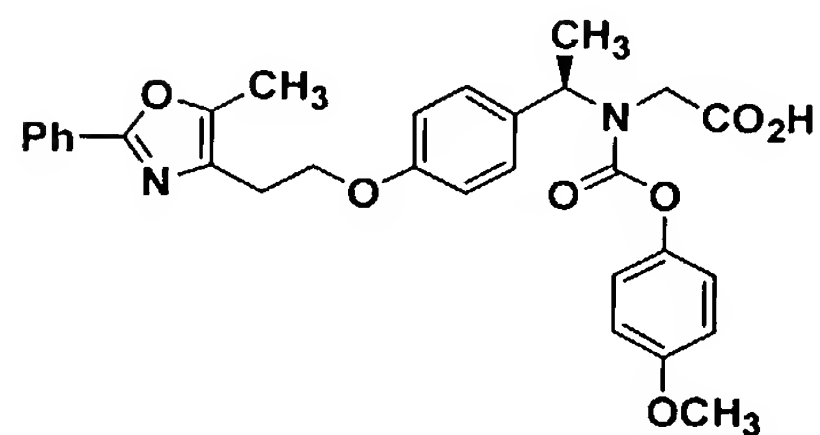
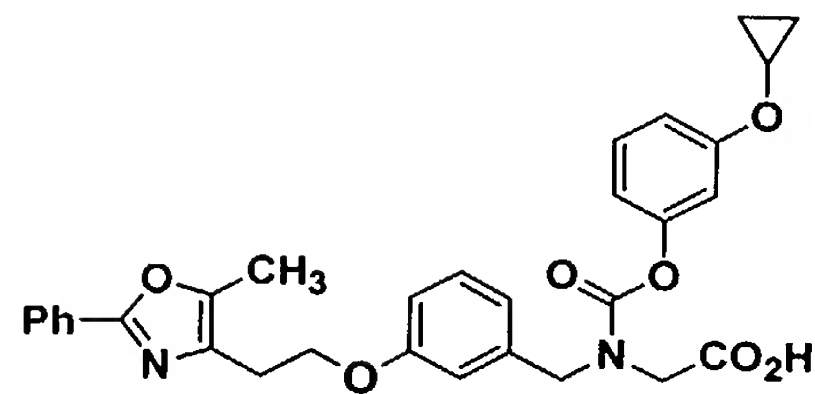
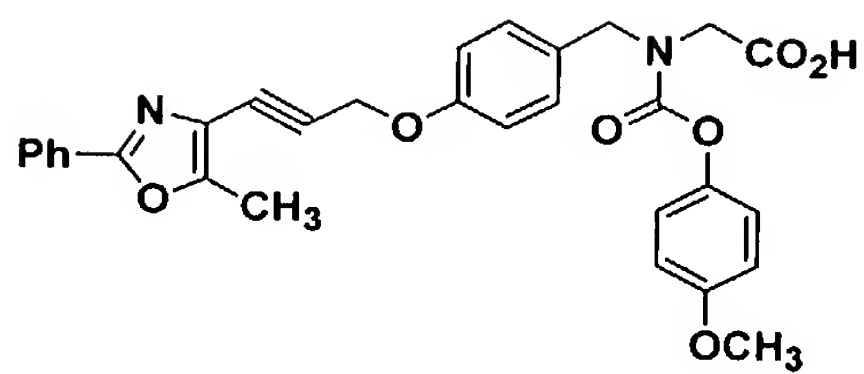


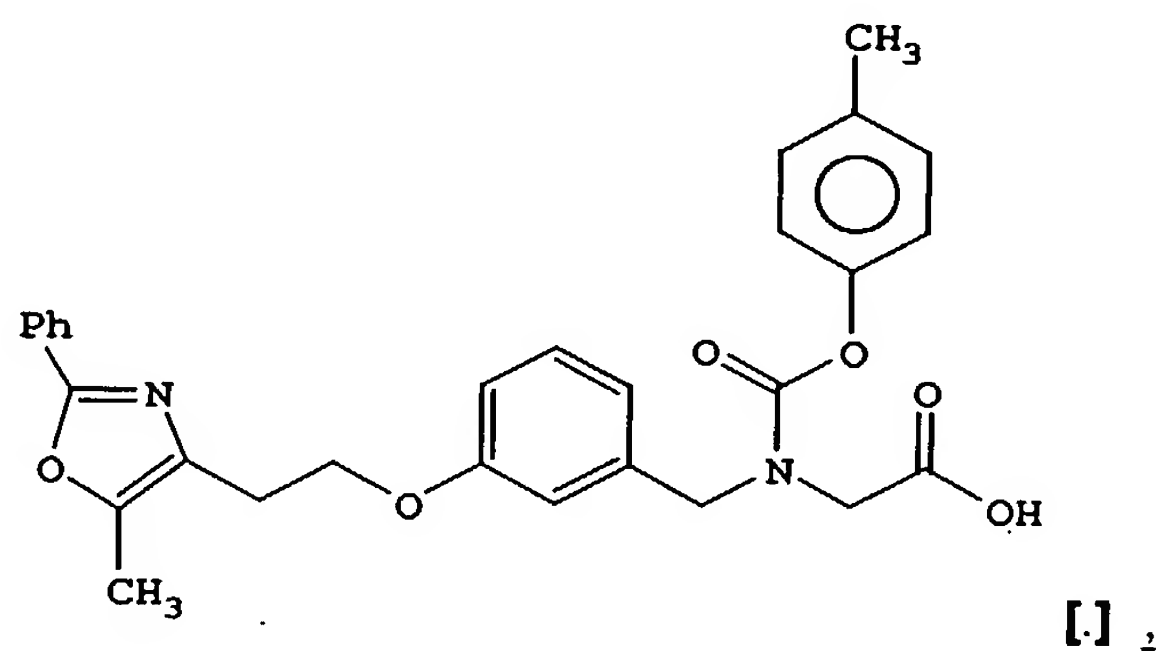
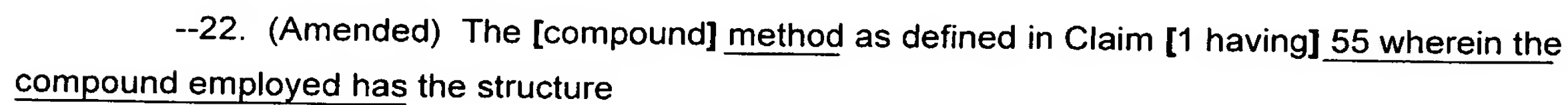
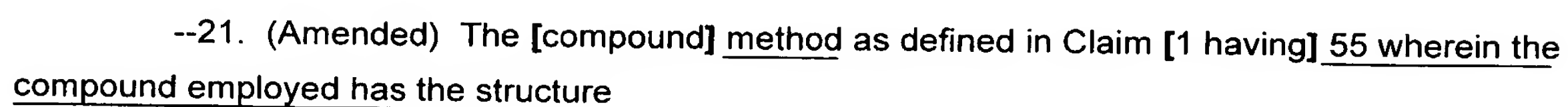


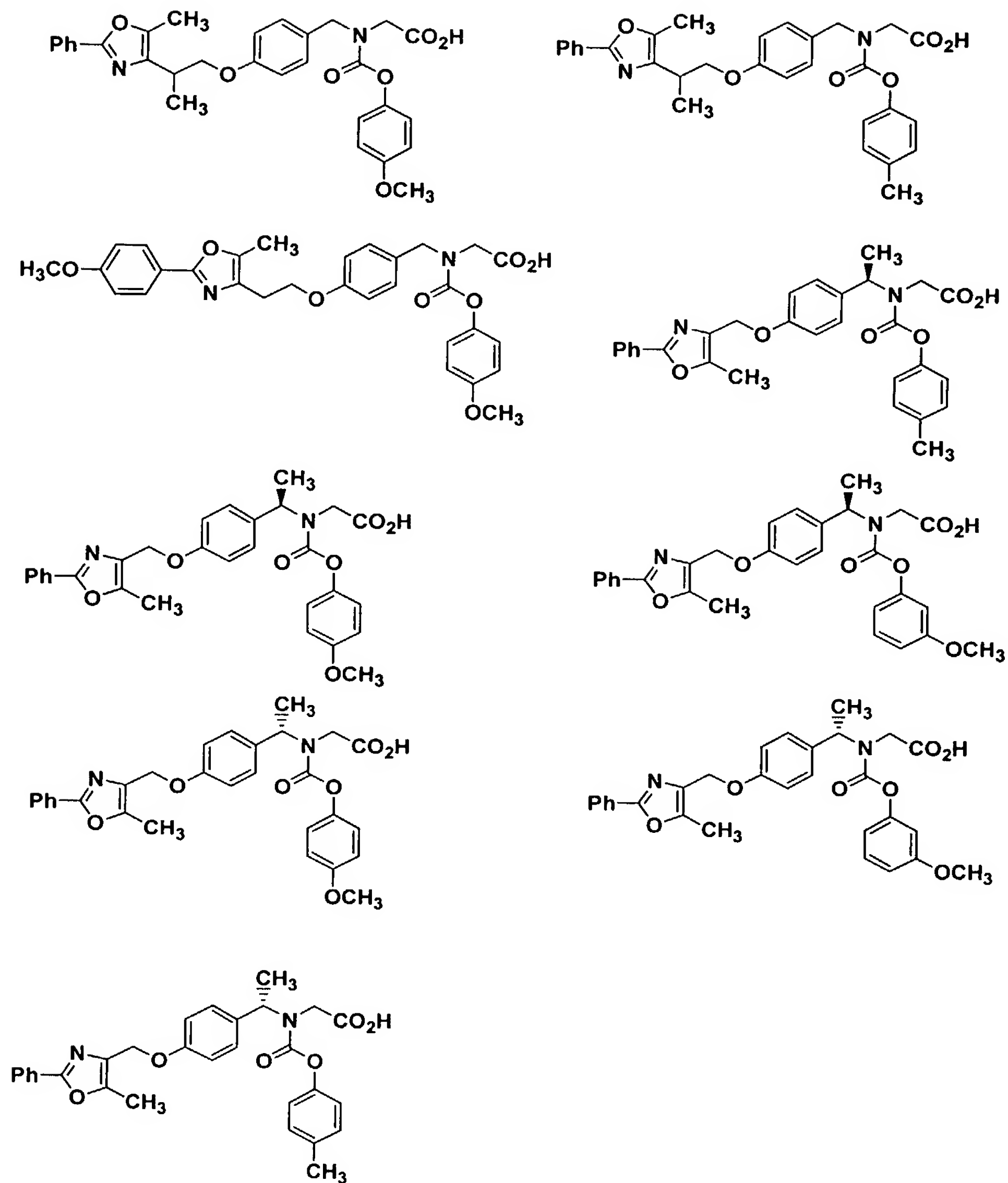
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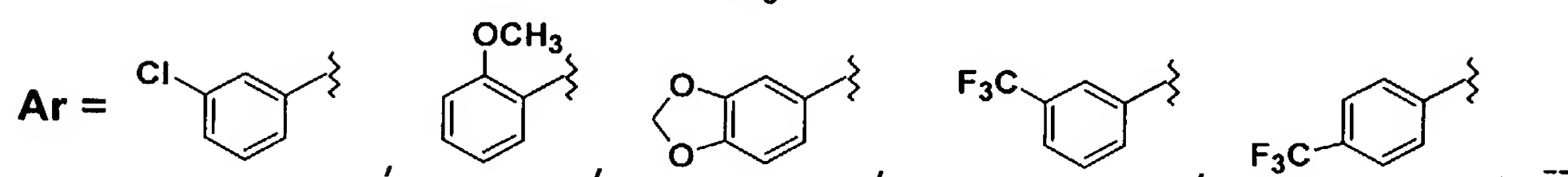
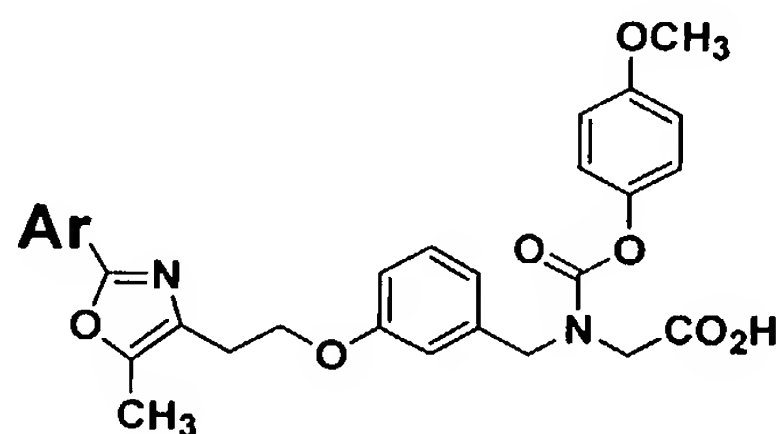
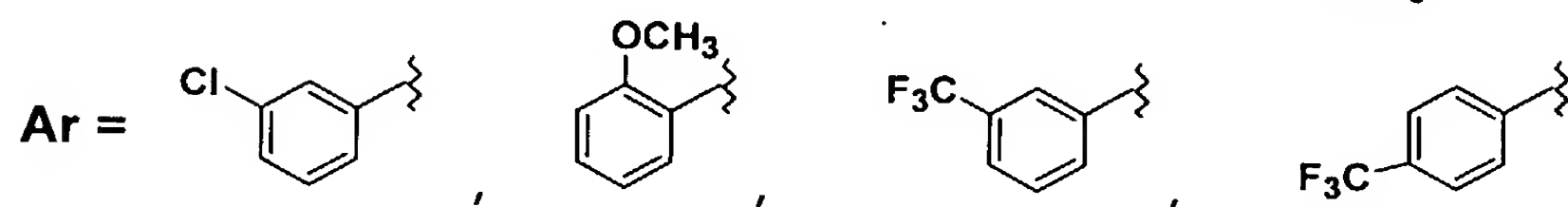
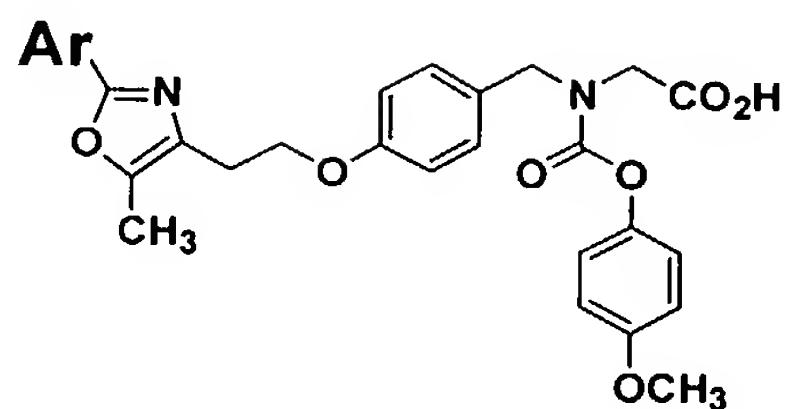
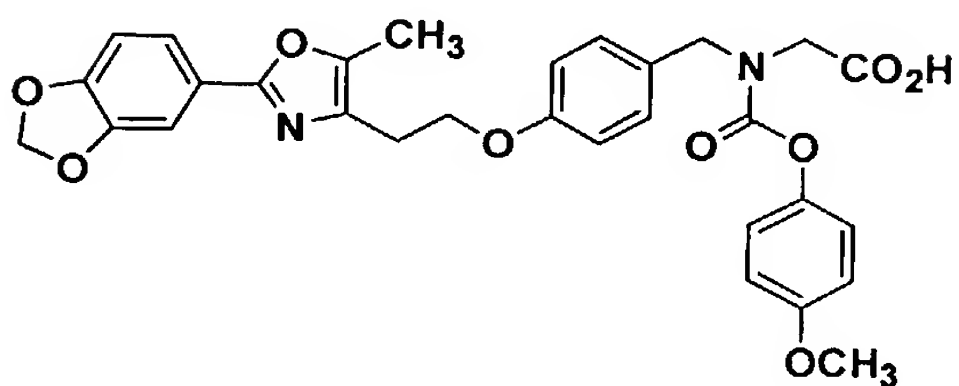
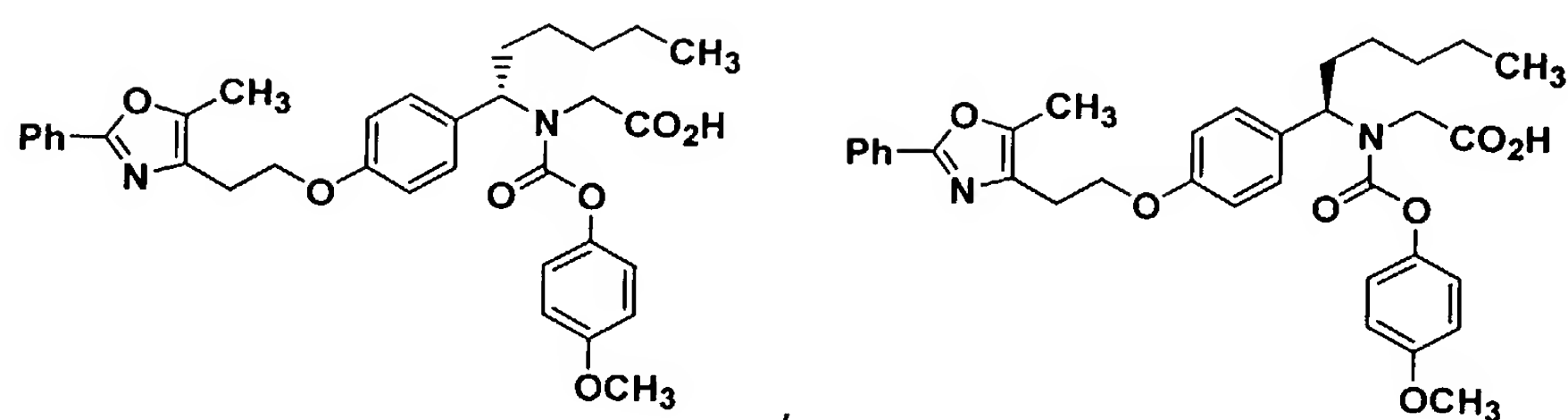


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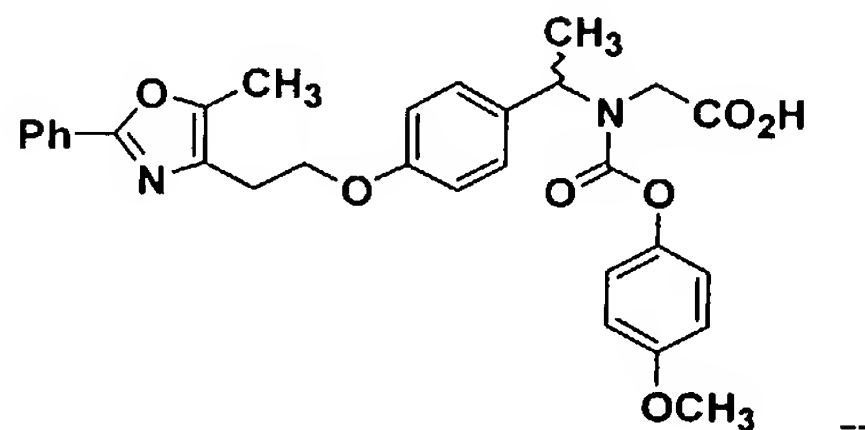




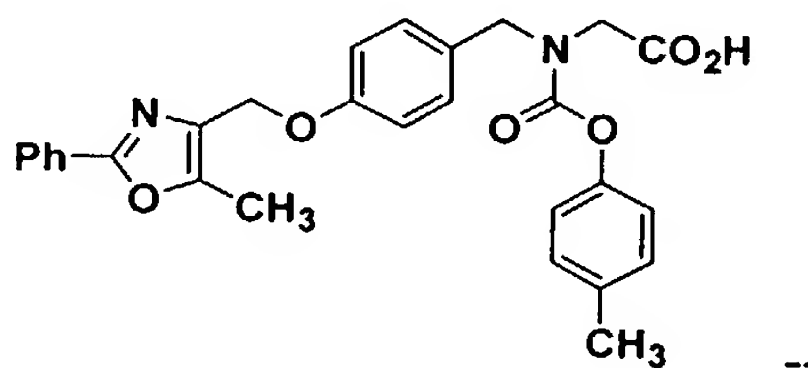


--21. (Amended) The [compound] method as defined in Claim [1 having] 55 wherein the compound employed has the structure

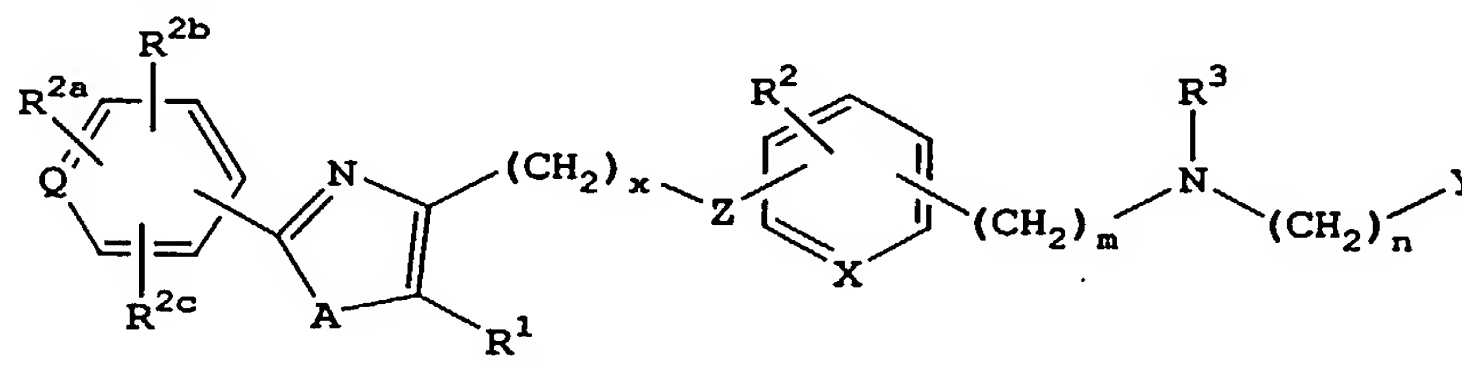
--31. (Amended) The [compound] method as defined in Claim [1 having] 55 wherein the compound employed has the structure



--32. (Amended) The [compound] method as defined in Claim [1 having] 55 wherein the compound employed has the structure



--34. (Amended) A method for lowering blood glucose levels or for treating diabetes, or for treating a premalignant disease, an early malignant disease, a malignant disease or a dysplastic disease, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound [as defined in Claim 1] which has the structure



wherein x is 1,2, 3 or 4; m is 1 or 2; n is 1 or 2;

Q is C or N;

A is O or S;

Z is O or a bond;

R<sup>1</sup> is H or lower alkyl;

X is CH;



R<sup>2</sup> is H, alkyl, alkoxy, halogen, amino or substituted amino;

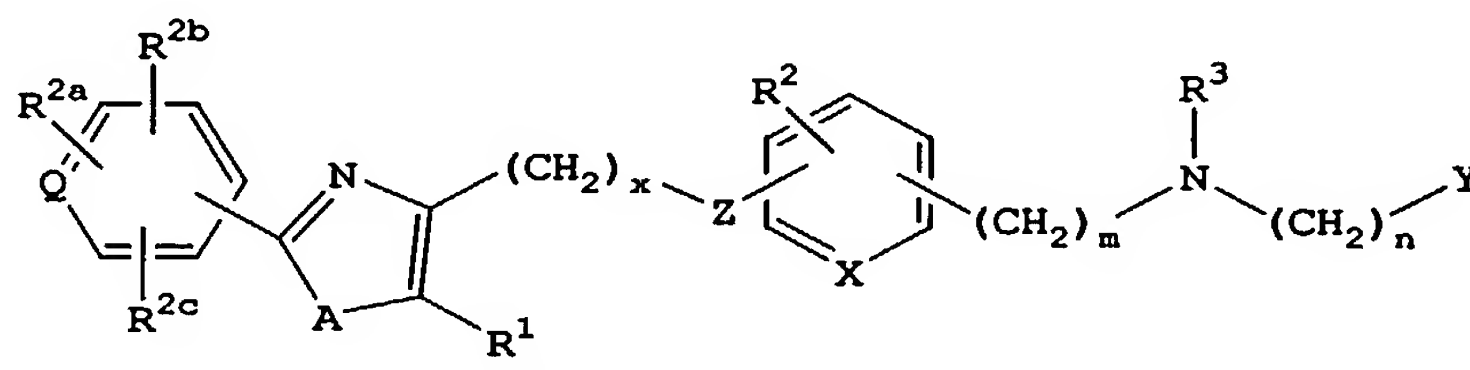
R<sup>2a</sup>, R<sup>2b</sup> and R<sup>2c</sup> are the same or different and are selected from H, alkyl, alkoxy, halogen, amino or substituted amino;

R<sup>3</sup> is aryloxycarbonyl, alkyloxycarbonyl, alkynyloxycarbonyl, alkenyloxycarbonyl, alkyl(halo)aryloxycarbonyl, alkyloxy(halo)aryloxycarbonyl cycloalkylaryloxycarbonyl, cycloalkyloxyaryloxycarbonyl, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, alkoxy carbonylamino, aryloxycarbonylamino, heteroaryloxycarbonylamino, alkylsulfonyl, alkenylsulfonyl, heteroaryloxycarbonyl, cycloheteroalkyloxycarbonyl, heteroarylalkenyl, hydroxyalkyl, alkoxy, alkoxyaryloxycarbonyl, arylalkyloxycarbonyl, alkylaryloxycarbonyl, alkynyloxycarbonyl, haloalkoxyaryloxycarbonyl, alkoxy carbonylaryloxycarbonyl, aryloxyaryloxycarbonyl, arylalkenyloxycarbonyl, heteroaryloxyarylalkyl, aryloxyarylalkyloxycarbonyl, aryloxyalkyloxycarbonyl, arylalkylsulfonyl, arylthiocarbonyl, arylalkenylsulfonyl, heteroarylsulfonyl, arylsulfonyl, heteroarylalkoxycarbonyl, heteroarylalkyloxyarylalkyl, arylalkenylarylalkyl, arylalkoxycarbonylheteroarylalkyl, heteroaryloxyarylalkyl, arylalkenylheteroarylalkyl or polyhaloalkylaryloxycarbonyl;

Y is CO<sub>2</sub>R<sup>4</sup> where R<sup>4</sup> is H or alkyl, or a prodrug ester or Y is a C-linked 1-tetrazole, a phosphinic acid of the structure P(O)(OR<sup>4a</sup>)R<sup>5</sup> here R<sup>4a</sup> is H or a prodrug ester, R<sup>5</sup> is alkyl or aryl or a phosphonic acid of the structure P(O)(OR<sup>4a</sup>)<sub>2</sub> where R<sup>4a</sup> is H or a prodrug ester;

or stereoisomers thereof, prodrug esters thereof, and pharmaceutically acceptable salts thereof. --

--37. (Amended) A pharmaceutical combination comprising a compound which has the structure



wherein x is 1,2, 3 or 4; m is 1 or 2; n is 1 or 2;

Q is C or N;

A is O or S;

Z is O or a bond;

R<sup>1</sup> is H or lower alkyl;

X is CH;

R<sup>2</sup> is H, alkyl, alkoxy, halogen, amino or substituted amino;

R<sup>2a</sup>, R<sup>2b</sup> and R<sup>2c</sup> are the same or different and are selected from H, alkyl, alkoxy, halogen, amino or substituted amino;

R<sup>3</sup> is aryloxycarbonyl, alkyloxycarbonyl, alkynyloxycarbonyl, alkenyloxycarbonyl, alkyl(halo)aryloxycarbonyl, alkyloxy(halo)aryloxycarbonyl, cycloalkylaryloxycarbonyl, cycloalkyloxyaryloxycarbonyl, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, alkoxy carbonylamino, aryloxycarbonylamino, heteroaryloxycarbonylamino, alkylsulfonyl, alkenylsulfonyl, heteroaryloxycarbonyl, cycloheteroalkyloxycarbonyl, heteroarylalkenyl, hydroxyalkyl, alkoxy, alkoxyaryloxycarbonyl, arylalkyloxycarbonyl, alkylaryloxycarbonyl, alkynyloxycarbonyl, haloalkoxyaryloxycarbonyl, alkoxy carbonylaryloxycarbonyl, aryloxyaryloxycarbonyl, arylalkenyloxycarbonyl, heteroaryloxyarylalkyl, aryloxyarylalkyloxycarbonyl, aryloxyalkyloxycarbonyl, arylalkylsulfonyl, arylthiocarbonyl, arylalkenylsulfonyl, heteroarylsulfonyl, arylsulfonyl, heteroarylalkoxycarbonyl, heteroarylalkyloxyarylalkyl, arylalkenylarylalkyl, arylalkoxycarbonylheteroarylalkyl, heteroaryloxyarylalkyl, arylalkenylheteroarylalkyl or polyhaloalkylaryloxycarbonyl;

Y is CO<sub>2</sub>R<sup>4</sup> where R<sup>4</sup> is H or alkyl, or a prodrug ester or Y is a C-linked 1-tetrazole, a phosphinic acid of the structure P(O)(OR<sup>4a</sup>)R<sup>5</sup> where R<sup>4a</sup> is H or a prodrug ester, R<sup>5</sup> is alkyl or aryl or a phosphonic acid of the structure P(O)(OR<sup>4a</sup>)<sub>2</sub> where R<sup>4a</sup> is H or a prodrug ester;

or stereoisomers thereof, prodrug esters thereof, and pharmaceutically acceptable salts thereof [as defined in Claim 1] and a lipid-lowering agent, a lipid modulating agent, an antidiabetic agent, an anti-obesity agent, an antihypertensive agent, a platelet aggregation inhibitor, and/or an antiosteoporosis agent. --

--39. (Amended) The combination as defined in Claim [38] 37 wherein the antidiabetic agent is 1, 2, 3 or more of a biguanide, a sulfonyl urea, a glucosidase inhibitor, a PPAR $\alpha$  agonist, a PPAR  $\gamma$  agonist, a PPAR  $\alpha/\gamma$  dual agonist, an SGLT2 inhibitor, a DP4 inhibitor, an aP2 inhibitor, an insulin sensitizer, a glucagon-like peptide-I (GLP-I), insulin and/or a meglitinide; the anti-obesity agent is a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake inhibitor, a thyroid receptor agonist, an aP2 inhibitor and/or an anorectic agent; the lipid lowering agent is an MTP inhibitor, an HMG CoA reductase inhibitor, a squalene synthetase inhibitor, a fibric acid derivative, an upregulator of LDL receptor activity, a lipoxxygenase inhibitor, or an ACAT

--40. (Amended) The combination as defined in Claim 39 wherein the antidiabetic agent is 1, 2, 3 or more of metformin, glyburide, glimepiride, glipyrice, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, troglitazone, rosiglitazone, insulin<sup>1</sup>, GI-262570, isaglitazone, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinide, nateglinide, KAD1129, AR-HO39242, GW-409544, KRP297, AC2993, LY315902, P32/98 and/or NVP-DPP-728A; the anti-obesity agent is orlistat, ATL-962, AJ9677, L750355, CP331648, sibutramine, topiramate, axokine, dexamphetamine, phentermine, phenylpropanolamine, and/or mazindol; the lipid lowering agent is pravastatin, lovastatin, simvastatin, atorvastatin, cerivastatin, fluvastatin, itavastatin, visastatin, fenofibrate, gemfibrozil, clofibrate, avasimibe, TS-962, MD-700, cholestagel, niacin and/or LY295427; the antihypertensive agent is an ACE inhibitor which is captopril, fosinopril, enalapril, lisinopril, quinapril, benazepril, fentiapril, ramipril or moexipril; an NEP/ACE inhibitor which is omapatrilat, [S[(R\*,R\*)]-hexahydro-6-[(2-mercapto-1-oxo-3-phenylpropyl)amino]-2,2-dimethyl-7-oxo-1H-azepine-1-acetic acid (gemopatrilat) or CGS 30440;

--50. (Amended) A method for treating insulin resistance, hyperglycemia, hyperinsulinemia, or elevated blood levels of free fatty acids or glycerol, hyperlipidemia, obesity, Syndrome X, dysmetabolic syndrome, inflammation, diabetic complications, impaired glucose homeostasis, impaired glucose tolerance, hypertriglyceridemia, [or] atherosclerosis, or for treating irritable bowel syndrome, Crohn's disease, gastric ulceritis or osteoporosis, or psoriasis, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a pharmaceutical combination as defined in Claim [43] 37. --

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\*c1cc2oc(cc2n1Cc3ccccc3)OCCOc4ccc(cc4)CNC(C)(C)CC(=O)O

(CH<sub>2</sub>)<sub>m</sub> is CH<sub>2</sub> or  $\begin{array}{c} \text{CH}_3 \\ | \\ \text{---CH---} \end{array}$  and R<sup>3</sup> is aryloxycarbonyl or alkoxyaryloxycarbonyl.

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